Fifth International Congress on Diseases of the Chest
Tokyo, Japan — September 7-11, 1958

VOLUME XXXIV NUMBER 2

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

PUBLISHED MONTHLY

AUGUST
1958

PUBLICATION OFFICE, CHICAGO, ILLINOIS

EXECUTIVE OFFICE, 112 EAST CHESTNUT STREET, CHICAGO 11, ILLINOIS

Entered as Second Class Matter at the Postoffice at Chicago, Illinois

3 essential drugs for chemotherapy of tuberculosis

NYDRAZID

Squibb Isoniazid

The most potent anti-tuberculosis agent available—developed in Squibb Laboratories.

Tablets, 50 and 300 mg., bottles of 100 and 1000
Syrup, 10 mg. per ml., pint bottles
Injection, 100 mg. per ml., 10 ml. vials

DISTRYCIN

Squibb Streptodusein

As active as streptomycin or dihydrostreptomycin, but with markedly less toxicity.

Powder, vials containing 1 Gm. and 5 Gm.
Solution, 0.5 Gm. per ml., vials of 2 ml. and 10 ml.
0.5 Gm. per 1.25 ml., vials of 2.5 ml. and 12.5 ml.

REZIPAS

Squibb PAS Resin

Many patients unable to tolerate PAS can take Rezipas.

1 pound jars

SQUIBB

A PIONEER IN ANTI-TUBERCULOSIS RESEARCH

DISEASES *of the* CHEST

OFFICIAL PUBLICATION

OF THE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE

112 East Chestnut Street, Chicago 11, Illinois, U.S.A.

MURRAY KORNFELD, *Managing Editor*

WARD BENTLEY, *Business Manager*

VOLUME XXXIV AUGUST, 1958 NUMBER 2

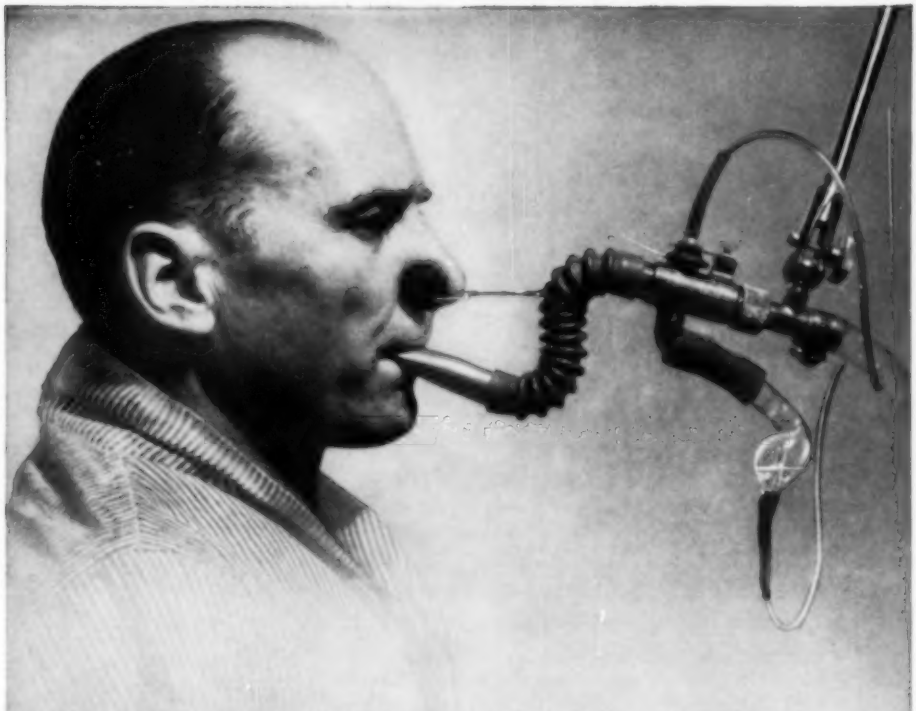
CONTENTS

SECTION ON CARDIOVASCULAR DISEASES

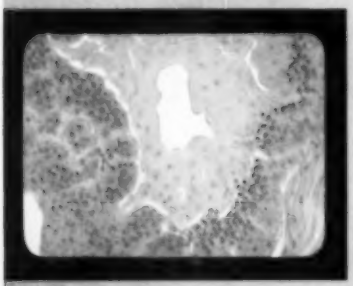
CASE REPORT SECTION

Entered as Second Class Matter at the Postoffice at Chicago, Illinois

Annual Subscription: $15.00, postpaid to any part of the world.



liquefy mucopurulent exudates in minutes



ACTION—specifically lyses desoxyribonucleoprotein, one of the major components of purulent bronchial secretions.

BENEFITS—enzymatic action starts on contact with mucopurulent exudates . . . does not degrade living tissue . . . is better tolerated than streptococcal desoxyribonuclease.

ADMINISTRATION—via aerosol therapy with or without antibiotics or bronchodilators.

INDICATIONS: Purulent bronchitis, bronchiectasis, atelectasis, emphysema, unresolved pneumonia and chronic bronchial asthma; as an adjunct in the diagnosis of bronchogenic carcinoma.

SUPPLIED: Each combination package contains one vial of lyophilized pancreatic dornase (100,000 units) and one 2 cc. vial of sterile diluent.

Dornavac®

(Pancreatic Dornase)

MERCK SHARP & DOHME Division of MERCK & CO., Inc., Philadelphia 1, Pa.

MSD

THE ECONOMICS OF SIDE EFFECTS

In tuberculosis therapy, use of the usual PAS compounds – the free acid or its sodium salt–very frequently leads to side effects or unwelcome reactions that jeopardize the overall aim of therapy . . . the patient's rapid return to normal living. Of considerable and often overlooked importance–particularly to the TB hospital and its staff – is the effect that such undesirable patient reactions to PAS administration have on the total cost of treatment:

UNDESIRABLE REACTIONS (PASA & NaPAS)	ECONOMIC RAMIFICATION
Anorexia, nausea, vomiting (present in approximately half of patients)[1]	*1. Cost of prepared but untouched or wasted meals.* *2. Extra physician or nursing time to cope with intolerance problem.* *3. Patient resistance leading to wastage of medication.*
Toxicity, sensitization or complete intolerance	*1. More prolonged hospital stay.* *2. Overall cost of special care by physician, nurse and pharmacist– desensitization, dosage adjustment, etc.*
Patient resistance to PAS form and dosage regimen	*1. Cost of medication thrown away by the patient.* *2. More prolonged hospitalization resulting from inadequate dosage.*

For this large group of problem patients (therapeutically and–consequently–economically) PASKALIUM (KPAS) provides the answer:

- Incidence of anorexia, nausea, vomiting and diarrhea extremely low (less than 7%) [1,2]
- No incidence of toxicity[1,2]
- Sensitization and complete intolerance less than 5%[1,2]
- Patient cooperation–the new capsule dosage form basically overcomes patient resistance to taste and most other undesirable aspects of PAS dosage.

Although PASKALIUM is more expensive initially (approximately $ .12 more per patient per day) than the lowest cost form of PAS it should prove vastly more economical when all factors of anti-tuberculosis therapy are considered.

1. Molthan, L., Cohen, R.V., and Zarafonetis, C.J.D.: Am. Rev. Tuber. 71:220, 1955.
2. Cohen, R.V., Molthan, L., and Zarafonetis, C.J.D.: Dis. Chest 30:418, 1956.

GLENWOOD LABORATORIES, INC., BERGENFIELD, NEW JERSEY

When anxiety and tension complicate **HIGH BLOOD PRESSURE**

Treatment is more successful when mental pressure and blood pressure are treated together **Miltown**

Miltown in addition to ganglionic blocking therapy resulted in subjective and objective improvement in 35 of 37 patients. On the antihypertensive agent alone, only 28 patients improved.[1]

Literature and samples on request

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

The original meprobamate, discovered and introduced by WALLACE LABORATORIES, *New Brunswick, N. J.* cm-6710

• • • *These outstanding lecturers will participate in this postgraduate course:*

WILLIAM E. ADAMS, Chicago
ALBERT H. ANDREWS, Chicago
ANDREW L. BANYAI, Chicago
ALVAN L. BARACH, New York City
BENJAMIN BOSHES, Chicago
JOHN F. BRIGGS, St. Paul
CHARLES CRUMPTON, Madison, Wis.
DAVID CUGELL, Chicago
HOWARD G. DAYMAN, Buffalo, N. Y.
DAVID DRESDALE, Brooklyn, N. Y.
EGBERT H. FELL, Chicago
WARD S. FOWLER, Rochester, Minn.
EDWARD A. GAENSLER, Boston
BENJAMIN M. GASUL, Chicago
ROY F. GODDARD, Albuquerque
BURGESS L. GORDON, Albuquerque
JOHN S. GRAETTINGER, Chicago
DONALD B. GREGG, Washington, D. C.
GEORGE A. HELLMUTH, Milwaukee
ROSS C. KORY, Milwaukee
EDWIN R. LEVINE, Chicago
ULRICH C. LUFT, Albuquerque
ALDO A. LUISADA, Chicago
IRVING MACK, Chicago
GEORGE R. MENEELY, Nashville
HURLEY L. MOTLEY, Los Angeles
OGLESBY PAUL, Chicago
JOHN F. PERKINS, JR., Chicago
COLEMAN B. RABIN, New York City
MAX S. SADOVE, Chicago
GEORGE SAXTON, Chicago
MAURICE S. SEGAL, Boston
GORDON L. SNIDER, Chicago
DAVID M. SPAIN, Brooklyn, N. Y.
PETER A. THEODOS, Philadelphia
JOSEPH F. TOMASHEFSKI, Columbus

American College of Chest Physicians
112 East Chestnut Street
Chicago 11, Illinois

I wish to enroll in the Chicago Postgraduate Course on CLINICAL CARDIOPULMONARY PHYSIOLOGY, October 13-17, 1958. Enclosed is my tuition fee.

Please Check
☐ Member—$75. ☐ Non-Member—$100.

NAME_____

ADDRESS_____

CITY/STATE_____

Registration is limited. Applications will be accepted in the order received.

Pfizer family of antituberculosis agents meets all case requirements

VIOCIN® (Brand of viomycin sulfate)
COMBISTREP® (Brand of streptoduocin)
STREPTOHYDRAZID® (Brand of streptomycylidene isonicotinyl hydrazine sulfate)
STREPTOMYCIN SULFATE DRY POWDER
STREPTOMYCIN SULFATE SOLUTION
Also available in Steraject® cartridge.
DIHYDROSTREPTOMYCIN SULFATE DRY POWDER
DIHYDROSTREPTOMYCIN SULFATE SOLUTION
Also available in Steraject cartridge.
COTINAZIN® (Brand of isoniazid)
TERRAMYCIN® (Brand of oxytetracycline)

References: **1.** Shubin, H., and Heiken, C. A.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia, Inc., 1956, p. 173. **2.** Ross, J. D.; Horne N. W.; Grant, W. B., and Crofton, J. W.: Brit. M. J. *1*:5065 (Feb. 1) 1958. **3.** Kass, I.; Russell, W. F., Jr.; Heaton, A.; Miyamoto, T.; Middlebrook, G., and Dressler, S. H.: Ann. Int. Med. *47*:744 (Oct.) 1957. **4.** Feldmann, F. M., Medical Director, National Tuberculosis Association: Pediatrics *21*:319 (Feb.) 1958.

the Pfizer family of antituberculosis drugs... for the family with the tuberculosis problem

The Grandfather, aged 60, had **chronic fibro-ulcerative pulmonary tuberculosis with reactivation;** resistant organisms.

Therapy STREPTOHYDRAZID with COTINAZIN.

Because After 15 months of therapy, 77% of these patients show clinical and/or roentgenographic improvement.[1]

The Mother, aged 33, had **moderately advanced tuberculosis with persistent cavitation;** resistant organisms; required resection.

Therapy VIOCIN and TERRAMYCIN.

Because With the use of the newer drugs, such as Viocin, combined with Terramycin, "operative procedures can be carried out successfully."[2]

The Father, aged 35, had a new case of **active pulmonary tuberculosis** with susceptible organisms.

Therapy COTINAZIN and STREPTOMYCIN.

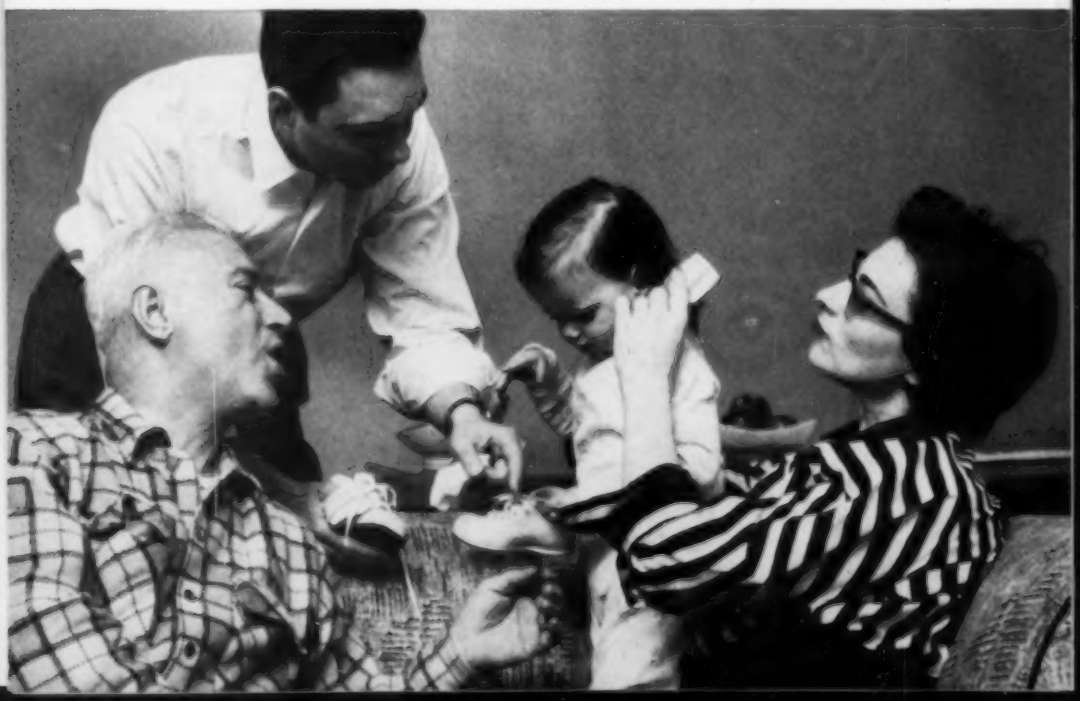
Because "We have not as yet encountered a therapeutic failure on this program, in patients excreting organisms initially susceptible to the drugs employed."[3]

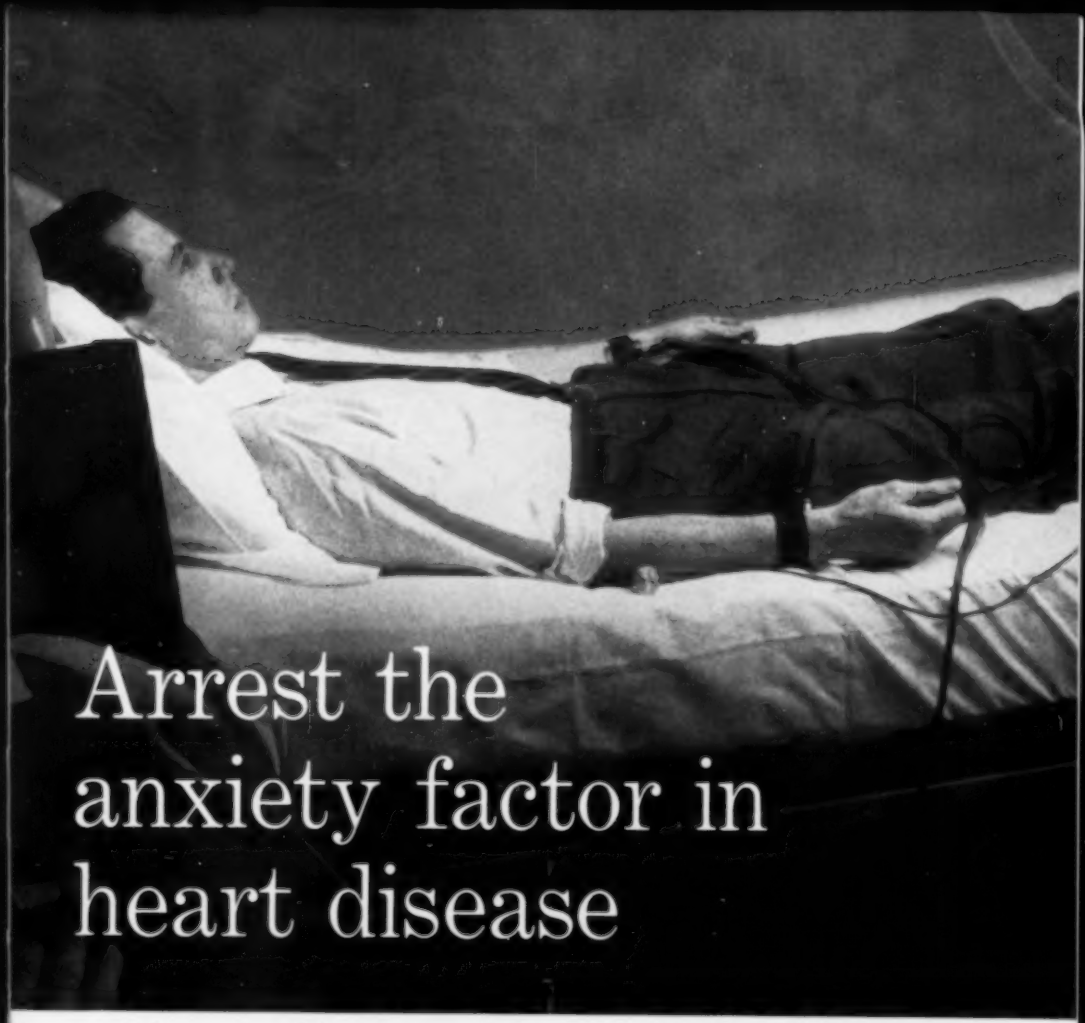
The Grandchild, aged 2, was a recent **tuberculous converter.**

Therapy COTINAZIN, may be combined with another agent.

Because Studies of Cotinazin prophylaxis in primary tuberculosis have confirmed the considerably reduced risk of future disease in tuberculin reactors among children.[4]

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.,* Brooklyn 6, N. Y.





Arrest the anxiety factor in heart disease

without affecting autonomic function

"A cardiac breakdown might be forestalled or arrested" by effective treatment of nervous tension and anxiety.* ■ Adjunctive therapy with meprobamate "definitely reduced nervous tension and anxiety" in all heart patients (80 cases), and enhanced recovery from acute cardiac episodes in many cases.*

Because of its unexcelled safety, *Miltown is well suited for tranquilization of chronic heart patients. It is well tolerated, relatively nontoxic, and produces no blood dyscrasias, liver impairment, parkinsonism, or nasal stuffiness. It does not mask toxicity of other drugs.*

Miltown®

*Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.

Miltown is the original *meprobamate, discovered and introduced by* WALLACE LABORATORIES *New Brunswick, N. J.*

M-6970

PREVENT
both cause and fear of
ANGINA ATTACKS

"In diagnosis and treatment [of cardiovascular diseases] ...the physician must deal with both the emotional and physical components of the problem simultaneously."[1]

The addition of Miltown to PETN, *as in Miltrate, "...appears to be more effective than* [PETN] *alone in the control of coronary insufficiency and angina pectoris."*[2]

1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* 1:393, *March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* 8:504, *Dec. 1957.*

DISEASES of the CHEST

VOLUME XXXIV AUGUST, 1958 NUMBER 2

Pathologic Findings in Benign Pulmonary Histoplasmosis*

Preliminary Report—Part I†

HENRY C. SWEANY, M.D., F.C.C.P.,** DAVID GORELICK, M.D.,‡
FRED C. COLLER, M.D.‡ and JAMES L. JONES, H.T.§
Mt. Vernon, Missouri

Owing to its close mimicry of other diseases, histoplasmosis has escaped recognition as a common disease entity until about the last 15 years. After Darling's first report[1] in 1906, it was almost three decades before the full significance of his discovery was realized. The more important advances in the history of the disease have been given recently by Schwarz and Baum.[2] Without going into details, therefore, let it be stated that there have been several types of disease recognized ranging from the generalized and fulminating form to those with no symptom at all. The severe type was described by Darling and was considered by him and his immediate successors as almost always fatal. Although this type was uncommon, it probably was present under a masquerade of a rare septicemia or anemia. The various other clinical types of the disease have been given recently by Furcolow,[3] which are listed as the asymptomatic, mild, moderately severe, and severe types, with various subgroupings. One of the important aspects mentioned was the close similarity to tuberculosis.

Since this is primarily a pathologic study, the discussions will be confined chiefly to methods of identifying the disease and to pathology. The fulminating type of disease has been well documented by Darling and others. Generally there is reported a great profusion of histiocytes which are packed with small, round or oblong bodies having a small nucleus. The close resemblance to Kala-azar has been mentioned by Darling[4] and by Meleney.[5] One of the characteristics of this type of lesion is that it is almost purely a histiocytic reaction with no polymorphs, lymphocytes,

*From the Missouri State Sanatorium. We are deeply indebted to Dr. Charles A. Brasher, Medical Director, for unreserved support in this work.

It was the privilege and pleasure of one of us (S) to be accorded the courtesy of members of the Armed Forces Institute of Pathology, in Washington, D. C., where many valuable suggestions were made that helped to orient us in our studies. We are particularly grateful to Capt. Silliphant, Director of the Institute, and to Dr. S. H. Rosen, of the Pathological Department of Chest Diseases.

**Director of Research, Pathology and Allied Sciences.

†Presented in brief before the Chicago Pathological Society, May 13, 1957, and in full at the Am. Soc. Clin. Path. at New Orleans, Oct. 2, 1957.

‡Consulting Pathologist.

§Histological Technician.

A few specimens were from the Pathology Department of St. John's Hospital and Springfield Baptist Hospital, Springfield, Mo., where D. G. and F. C. are pathologists.

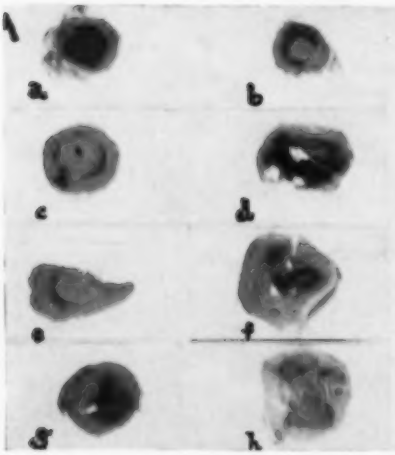


FIGURE 1

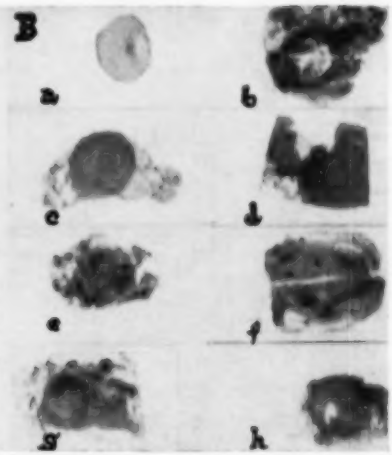


FIGURE 2

Figure 1: This is designated as A which represents typical histoplasmomas. They are to be contrasted with typical tuberculomas which are found in the B group. H & E Stain. a. M. S., A20—No. 24,674, is the stained section of a 1½ mm. spherical lesion from the lung parenchyma of a 57 year old housewife, negative tuberculin, strongly positive histo. skin reaction. Numerous yeast-like bodies were found. b. N. O., A30—No. 26,079, similar section from a 2½ cm. spherical lesion taken from the lung parenchyma of a 51 year old housewife. Both tuberculin and histo. skin tests were strongly positive. Innumerable yeast bodies were found in the central part of the lesion. c. E. S., A15—No. 24,493, similar section from the lung parenchyma of a 49 year old housewife. Tuberculin test was weakly positive, histo. skin test strongly positive. Large number of yeast bodies were found. d. M. B., A23—No. 25,217, similar section from a 46 year old housewife. Tuberculin test weakly positive, histo. skin test slightly more positive. Many yeast bodies found in the lesion. e. H. S., A9—No. 23,517, a 61 year old carpenter. Tuberculin weakly positive; histo. strongly positive. Many yeast bodies found. f. L. B., A21—No. 24,797, from the parenchyma of a 44 year old housewife. Tuberculin negative; histo. skin test weakly positive. A few yeast bodies were found. g. O. I., A12—No. 24,302, was the same from a 42 year old truck driver. Tuberculin and histo. skin tests were both weakly positive. There were many yeast bodies found. h. W. F., A41—No. S-0591 from St. John's Hospital. This is a 52 year old white male having lesion discovered on routine x-ray. A few typical yeast bodies were found.—*Figure 2:* Designated as B, represents 8 spherical lesions in which acid fast bacilli have been found and no yeast bodies. a. A47—No. X-117 from a 40 year old male taken many years ago in Chicago. This was a lesion quite similar to many of the lesions found in histoplasmosis. It seemed to have been built up from a central focus. Acid fast bacilli were found in the periphery. It shows that the two diseases run parallel in many respects. However, there are many more of this type that are histoplasmosis than are tuberculous. Another point is that in the center of the lesion the parasites of histoplasmosis appear to live longer and produce more caseation and calcification with actual growth of the parasites, whereas tubercle bacilli are usually smothered after a few years. b. B. S., A11—No. 23,701, a spherical lesion from a 19 year old housewife. Weakly positive tuberculin, negative histo. skin reaction. Acid fast bacilli found. c. C. J., A14—No. 26,118, from a 37 year old cafe manager. Both tuberculin and histo. skin tests were positive. Acid fast bacilli were found. d. G. P., A16—No. 24,645, from a 46 year old housewife. Tuberculin strongly positive, histo. not done. Many acid fast bacilli found. e. C. P., A6—No. 22,584, a 45 year old farmer, strongly positive tuberculin, histo. not done. Many acid fast bacilli found. f. A larger section from another spherical lesion in the same patient, in which AFB were found. g. I. C., A5—No. 22,206, strongly positive tuberculin, histo. test not done. Many acid fast bacilli were found. h. F. A., A25—No. 25,057, skin test, tuberculin negative. Histo. skin test weakly positive. Section from spherical lesion of a 38 year old housewife. Acid fast bacilli found. The A and B in these two figures are not to be confused with the same letters in the two main groups.

plasma cells, or other characteristics of an acute infectious process. The histiocytes of the lung, liver, spleen and lymph nodes of the body become packed with the dot-like forms that may be seen on almost any stain, but are sometimes easier to see when stained with the periodic acid of Schiff (P.A.S.) as used by Bauer,[5] later modified by Hotchkiss and McManus,[7] or Gridley's stain.[8] The Gomori method,[9] however, as recently applied by Grocott[10] to mycological forms, is far superior to all others tried up to this time. As the disease progresses and the circulation becomes shut off, caseation develops and where the focus approaches the bronchus, cavities may form. The lymphatics are always invaded. The blood vessels are nearly always penetrated resulting in a hematogenous dissemination involving the spleen, adrenals, liver, bone marrow and lymphatics. The best illustration of the fulminating infection is that seen in the mouse where the histiocytes are packed with yeast and many of the organs may be 10 to 20 times their normal size. More recently the pathology of various types of the disease has been given by Schwarz,[11] Meleney,[4] Pinkerton,[12] and especially Binford.[14]

*Material**

Our material consists of two clinical types: first, clinically inactive, circumscribed lesions (so-called "coin" lesions), and second, obviously clinically active disease. As will be seen later there are few if any cases with yeasts present even in encapsulated lesions that are completely inactive. Along with the definitely positive cases there were almost as many which were suspected of histoplasmosis at one time or another or were similar in appearance to the other lesions and which serve as controls.

In the first, or group A, as subsequently designated, there were 21 proven cases of histoplasmosis. (Six more have been found since this was written.) There were 11 others in which acid-fast bacilli were found in the sputum or on the excised specimens. Of the other five, one case had a typical primary tuberculous complex with a strongly positive tuberculin and a negative histo. skin reaction. Of the other four cases, three were probably histo., and one was undetermined, but was considered tuberculous in spite of a negative A.F.B. stain.

In Group B with clinically active disease, there were 16 cases positive for histoplasmosis by the staining method. (Eleven more have been found since this was written.) In 11 cases acid-fast bacilli were found either in the sputum before operation, or in the tissues after operation, or both. (*Four of these 11 had both acid-fast bacilli and H. capsulatum.*) One case had acid-fast bacilli and may also have had occult histoplasmosis, but no yeast bodies were found. There were three cases in doubt, but they had more evidence in favor of histoplasmosis than tuberculosis. There were three having a diagnosis of bronchogenic carcinoma in which no H. capsulatum were found on stained section. One case in particular that was classed as a "granuloma" had a strong histoplasmosis complement fixation

*All but three postmortem specimens were obtained from surgical resections performed by Dr. John W. Polk, Chief Surgeon; Dr. W. W. Buckingham, Chief Surgical Consultant; and Dr. José Cubiles, Chief Surgical Resident.

FIG. 3

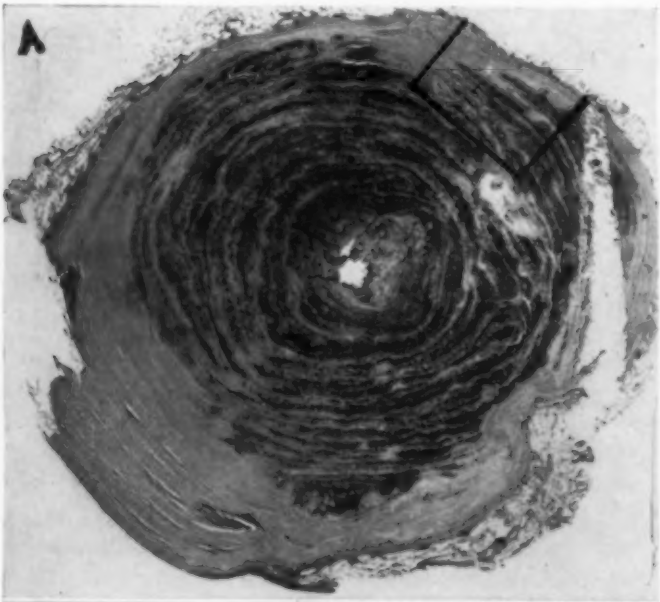


FIG. 4

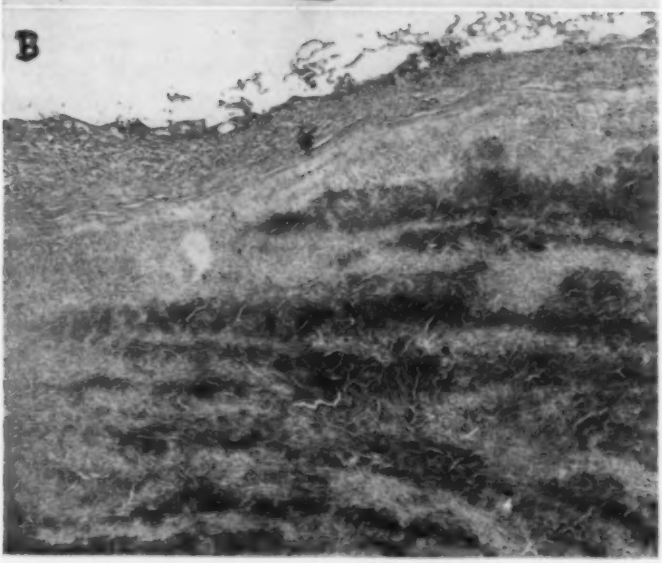


Figure 3: (A) A stained section of a spherical lesion of M. S., A39, S2037-55, showing the ring formation from the center outward. Note the heavy callous on one side. This heavy button-like plaque on one side is present on several spherical lesions and its cause is not understood. H. & E. × 4.5.—*Figure 4:* (B) A higher magnification of area marked off in Fig. 3. The calcification does not follow the fibrils, but is more related to distance from the center. H. & E. × 20.

reaction. Although the complement fixation reaction has been misleading in many cases, we feel that in this instance, where the reaction was present in a dilution of 1:128, the diagnosis of histoplasmosis was probably correct, but the case remained in the doubtful group.

Pathology

Since the material at our command is quite extensive, the present study will be in the nature of a preliminary report embracing the methods of study, tracing the course of the parasite in the body and roughly classifying the material in provisional groups, with a few illustrations of certain important features. In later studies we hope to describe the material more completely.

First are the circumscribed lesions that have sometimes been poorly designated as "coin lesions" because of the nummular appearance of the shadows on x-ray film and which may be considered under two headings for convenience: those that develop centrifugally from a small central focus, and those that are encapsulated infiltrates with a larger early localization of the infection. The third group consists of nodular lesions where the appearance ranges from a soft granuloma to fibrocaseous, calcific and calcific-ossified lesions. The fourth group is chronic pneumonitis with an early histiocytic infiltration and an early organizing fibrinous exudate which later develops into a granulomatous process with epithelioid cell proliferation and Langhan's giant cells. The fifth group consists of ulcerative lesions, acute caseo-ulcerative and fibroid, the latter with either cystic or dense cavity walls. The sixth group is bronchiectasis. The seventh is a pleuritic involvement. Finally, there is a mixed type of one or more of these various forms.

Descriptions of most of these eight groups will be given with a few illustrations.

The group of circumscribed lesions, although similar on x-ray film appearance, is quite varied on gross and microscopic appearance. There are at least two distinct types with several variations, depending on the development of the particular lesion. One definite type is the centrifugally-formed lesions which slowly spreads from a small focus and builds up around the edges like the layers of an onion. Sometimes the original focus may be found from which the process emanated. The low resistance of the host, or a special virulence of the parasite, or both, has accounted for the gradual formation of lesions, sometimes 3-4 cms. in diameter. Inasmuch as there are so many of these circumscribed forms in histoplasmosis, it is a fair index of the general sluggish but tenacious nature of the parasites in the human body in the chronic forms of the disease.

In the development of this lesion there are frequently alternating bands of fibrous tissue, one band containing many strands of long fibrils that are usually straight and encircle the focus. Next to this lies irregularly-formed tortuous fibrocytes of varying thickness and containing much collagen. These fibrocytes tend to undergo an early caseation and take on calcification giving the H. and E. stained section the laminated appearance of alternat-

ing dark and pink bands. Sometimes pockets of caseation may appear instead of the laminations. Whether the caseation is due to occult parasites or microspores of some type, or whether it develops as a result of a shut-

FIGURE 5 FIGURE 6

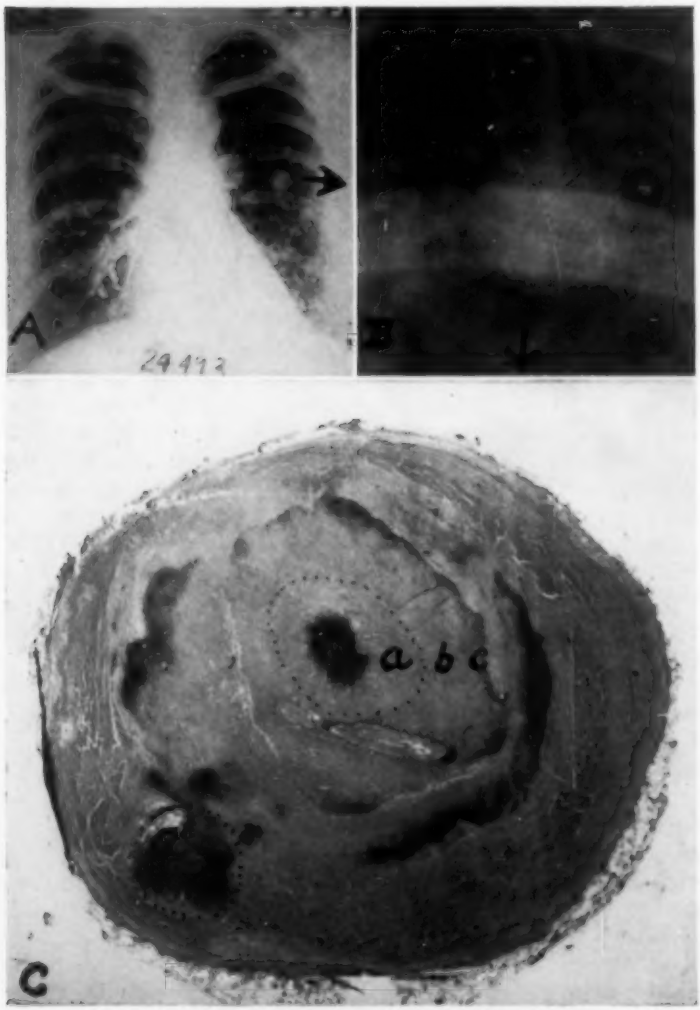


FIGURE 7

Figure 5: (A) A reduced roentgenogram of E. L. S., A-15, No. 24,493. Showing a spherical lesion in the left midfield with pleuritis at the left base and bronchiectasis in the right middle lobe.—*Figure 6:* (B) An enlargement of the spherical lesion of Fig. 5.—*Figure 7:* (C) A low power section of spherical lesion. Note the two centers of dense caseation and calcification outlined by small dots at a and a′ and the partial rings of less marked calcification.

ting-off of the circulation with death of the fibrocytes, is problematical. The fact is, that in most of these caseous foci are found the grayish-lavender stained bodies with the Gomori stain that are considered to be H. capsulatum. In this series, unless there were budding forms, a positive result was not recorded until a dozen or more of these stained bodies were found. There were several of these spherical lesions in which no caseation could be found and no parasites. Almost invariably the parasites were found only in caseous foci. In two lesions only three or four suspicious bodies were found. It was thought highly probable that some of them were the parasites of histoplasmosis, but there was not enough evidence for a certain diagnosis, and they were not counted as histoplasmosis.

Almost identical lesions are found in tuberculosis, although the "onion-ring formation" seems to be more pronounced in histoplasmosis—at least the true tuberculomata in this series were more homogeneous and less laminated, and had a greater tendency to ulceration. The differences are too slight to afford a dependable means of differentiating tuberculoma from histoplasmoma. The contrast of the two diseases is shown in figures 1 and 2.

Two histoplasmoma type lesions will be described; the first of a typical "onion-peel" formation.

M. S. A 41 S2037-55. The patient is a 52 year old white woman who entered St. John's Hospital on August 27, 1955. In 1952 she had a thyroidectomy done and stated that she had had a cough ever since this operation. She has also had hoarseness three months following the surgery. In May of 1955, an x-ray film was made and she was found to have a mass in the right upper lung field. She was advised to have surgery, but refused. She enters the hospital at this time for surgery. The physical examination revealed a well-healed thyroid scar with her cardiorespiratory system being negative. However, there was possibly a soft systolic murmur present at the apex. The balance of the physical examination was negative. At surgery a 6 cm. "tuberculoma" was found lying in the posterior segment of the right upper lobe. This was removed in a wedge resection. The mass measured 4 x 3 x 3 cm. It was extremely hard and also contained a gray-white plaque on the external surface. The plaque measured 12 x 10 mm. Beneath it there was a rounded tumor mass measuring 2 cm. in diameter. It contained a soft, central yellowish-gray core. Around this there were grayish-yellow laminations. The microscopic examination revealed a central area of calcified material with a wall of dense fibrous tissue. No cellular reaction was noted. There was occasionally a few lymphocytes seen. The adjacent pulmonary tissue was not remarkable. Diagnosis: "Tuberculoma" of the right upper lobe of the lung.

Comment: This case has every gross and microscopic characteristic of histoplasmosis, yet no yeast bodies were ever found. There was apparently a beginning focus near the center with a gradual build-up around the periphery, like winding a ball of twine. One outstanding feature, and one that may account for the absence of yeast bodies, was the absence of pockets of dense caseation. If yeasts were present, we did not find them, but it has been explained that a section 6 μ thick represents only about one two-thousandths of the whole mass. There may not have been the right conditions for formation of the caseation and consequently the "awakening" of the yeast bodies. The reason for the dense fibrosis on one side is not apparent. This was described as a "plaque 10x12 mm." This case is classed as a doubtful case, but from all appearances and past experiences in observing a large number of lesions it is probably histoplasmosis, since it is typical in every way except the presence of parasites.

At the present time we have no concrete answer to the question of why

these lesions do not show parasites yet they keep on expanding. There is something still lacking in our methods and in our knowledge of the disease.

FIGURE 8 FIGURE 9

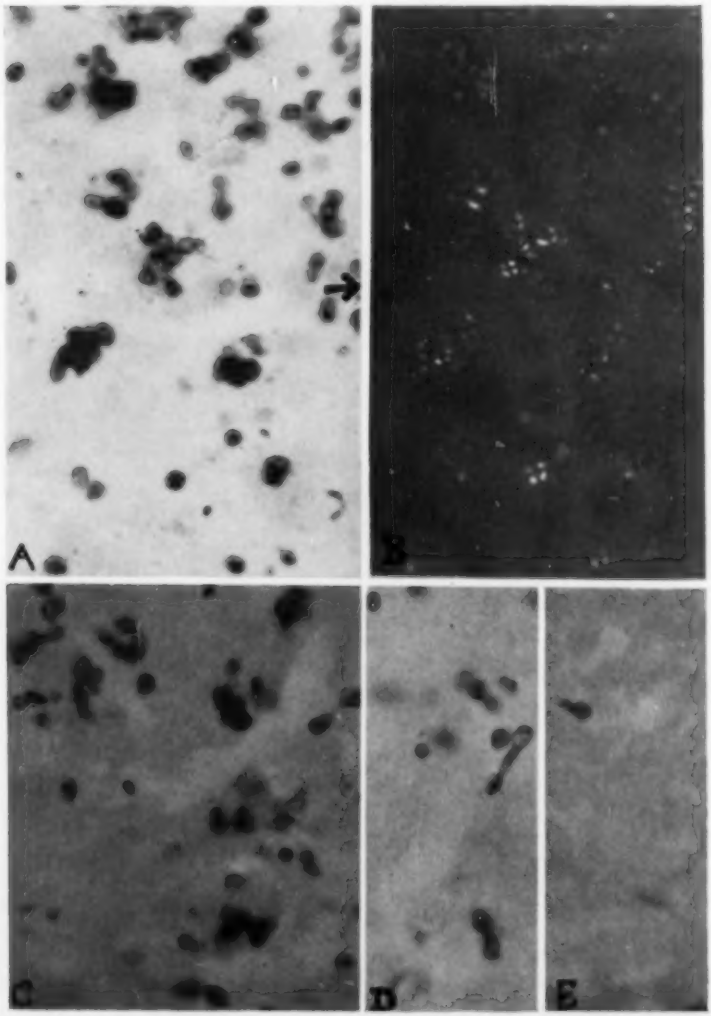


FIGURE 10 FIGURE 11 FIGURE 12

Figure 8: (A) A microscopic field of a G. M. S. stained section in the dense central, calcification marked at "a" in Fig. 7, showing innumerable yeast bodies. × 3400.—*Figure 9:* (B) A polariscopic view of same, showing "Maltese crosses." × 3400.—*Figure 10:* (C) A microscopic field of stained section extending outward into the zone marked "b" in Fig. 7. G. M. S. stain × 3400.—*Figure 11:* (D) A microscopic field of stained section still further out toward the periphery.—*Figure 12:* (E) Similar to Fig. (D.)

The Von Kossa calcium stain only exaggerated the findings observed on the H. and E. stain. There was no indication of an alveolar pattern as in the next case to be shown. The Von Kossa stain divides the field into the expanding type from one that represented an entrapped infiltrate.

Encapsulated infiltrates have an entirely different origin and appearance. These lesions are made up of pockets of caseation which probably emanated from larger collections of histocytes laden with parasites. Various fibrous bands separate many of these caseous foci in the central part of the lesion and around the periphery is a heavy layer of dense fibrous tissue that circumscribes the whole mass. Some of these may be the parenchymal forms of a primary lesion. Typical of this type is shown in the next case, Figs. 5, 6 and 7:

E. L. S. A-15 No. 24,493, was a 49 year old Pemiscot County housewife. She was exposed to a son who had tuberculosis. She was admitted to the hospital on February 27, 1955.

Her histo. skin test was positive 12/15 (12 mm. induration, 15 mm. erythema), weakly positive (3/5) for tuberculosis. All complement fixation tests for histoplasmosis were negative. All sputums were negative for acid fast bacilli and H. capsulatum. The x-ray film revealed a slight effusion at the left base and a spherical lesion in the left midfield of about 3 cm. in diameter. There also was found moderate bronchiectasis in the right middle lobe. A wedge resection was performed on April 12, 1955 to remove the dense round lesion.

The pathological examination revealed a solid fibroid mass 2-3 cm. in diameter. There was a slight softening with some calcifications in the center.

A G. M. S. stain revealed a remarkable distribution of many yeast bodies in the centers that showed the most caseation and calcification. There were hundreds in the central area with a diminishing number outward to the fibrous tissue. There were no full sized forms out near the margin, but many small forms measuring as small as 0.5 μ that polarized light and many still smaller that did not produce the usual Maltese cross on polarization. Some showed only a point of light, others showed nothing. A small focus of dense calcification out from the center revealed many budding parasites, but there were not as many as were in the central focus. The lighter crescent of calcification did not show any forms, large or small.

Comment: It is difficult to say what is the course of events in this type of lesion. From the appearance, however, it seems that the fibrous tissue becomes shut off from nourishment and gradually undergoes a chemical disintegration and caseation. Calcium ions slowly penetrate the mass and produce the insoluble calcium soaps in the form of a calcified matrix of varying degrees of density depending perhaps on the age of the process.

There appears to come a time when the conditions are suitable for the growth of the yeast bodies so that any dormant forms that were trapped at an earlier time will become active. From numerous observations these forms begin as small black ring bodies (approximately 0.5 μ in diameter) and gradually enlarge to 2, 3 and 5 mm. as the adult round to pear-shaped yeast. What the 0.4 μ, 0.3 μ and 0.2 μ forms can be is only speculation, but some of these small forms other than coal or iron particles appear also to be part of the yeast cycle. This theoretical concept fits the facts better than any other we have found. To suggest that the parasites come from without would be untenable because the mass is strictly avascular. The only thing left is to assume that some remain as resting residues (perhaps endospores) of active parasites of an earlier and active process. Some normal sized parasites may have persisted but the small microspores are still unaccounted for.

A most interesting feature was that the calcium stain (Von Kossa) reveals a remarkable pattern in the whole central area consisting of polygonal shaped patches that correspond to the original alveoli. The borders are made up of calcium-impregnated round bodies which might be due to a combination of the calcium with nucleic acid of the alveolar cell nuclei. This would indicate that instead of beginning as a small focus and building outward, the original focus was probably an infiltrate involving many alveoli. After the building up of the capsule the enlargement progressed the same.

The third group, or nodular type, ranges from a soft grayish mass that may vary from a millimeter or two up to 1½ cm. in diameter or to dense encapsulated and calcified and even ossified lesions. The soft lesion generally has more of a bluish-gray appearance than a tubercle of similar size, but this is not a sharp differentiation. The microscopic appearance resembles very much that of a caseous tubercle with a central area of debris surrounded by a hyalinized band of caseated fibrous tissue outside of which may be varying amounts of granulation tissue. Sometimes the lesions may be multiple as shown first by Christie and Peterson.[13] The central area of

FIG. 13

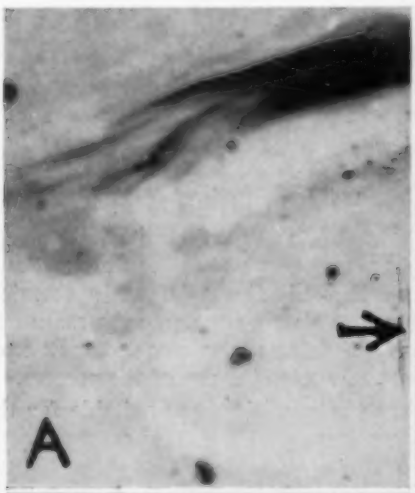


FIG. 14

FIG. 15

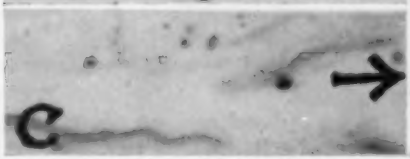


FIG. 16

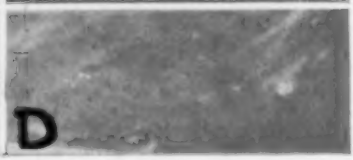


Figure 13: (A) A zone marked by "c" in Fig. 7 where there is still fibrous tissue. The dark staining bodies are smaller and assume a round granular appearance. Most show no birefringence, but one in upper left is typical. G. M. S. stain × 3400.—*Figure 14:* (B) Polariscopic view of Fig. 13. Only 2 or 3 show a faint birefringence. G. M. S. stain × 3400.—*Figure 15:* (C) Still further out in the fibrous tissue. G. M. S. stain × 3400. —*Figure 16:* (D) Polariscopic view of Fig. 15. Only one shows typical birefringence. Others only show points of light. They may be artefacts. × 3400.

these masses is usually less dense than that of a corresponding tubercle. There is a complete absence of polymorphonuclear leukocytes, lymphocytes and plasma cells, but occasionally red blood corpuscles may seep into the central area from the granulation tissue outside the wall. As pointed out by Binford[14] the capsule is commonly made up of a palisade-like arrange-

FIG. 17

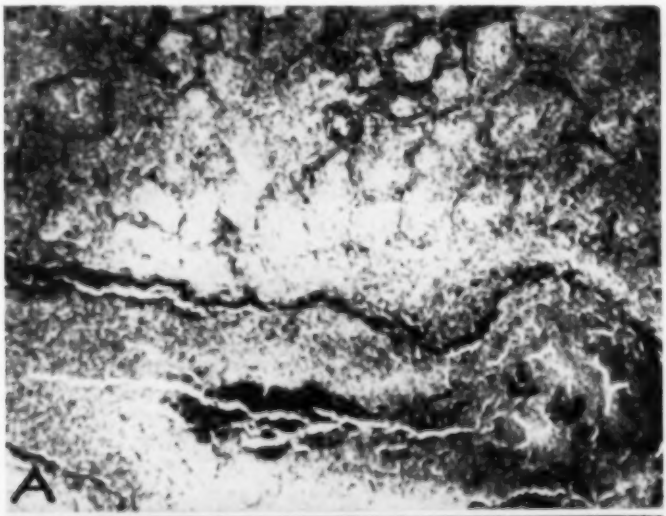


FIG. 18

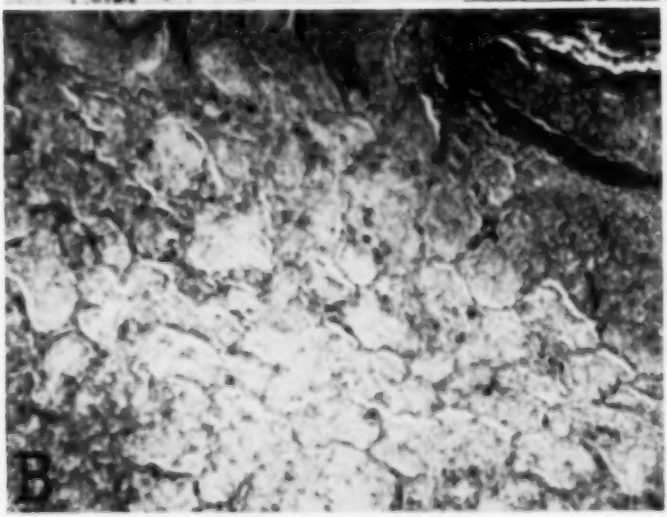


Figure 17: (A) A microphotograph of the central area of Fig. 7 (the blood vessel marks the general location). Note the outlines of the alveoli caused by the calcium deposits in the alveolar wall, and possibly to a calcium salt of nucleic acid in the disintegrated nuclei of the alveolar walls. × 48 Von Kossa stain.—*Figure 18:* (B) Another view similar to that of Fig. 16.

ment of cells pointing toward the center of the lesion. As these lesions become larger, a central crevice appears that expands into a cavity. Indentations may occur in the wall and a necrosis may extend far out into the tissue at one or several points around the periphery. The fibrous tissue usually becomes hyalinized. The central area is made of caseous debris, disintegrating red cells and macrophages, but no polymorphs or lymphocytes. There is generally a much thinner type of grayish necrotic pus than there is in caseous tubercles. Some of the lesions may become densely encapsulated and go through the same evolution as that observed in tuberculosis. The central area may become densely calcified and actually ossified, which represents lesions of more than a decade in age. In practically all these lesions we have found large numbers of the suspicious bodies that are thought to be H. capsulatum. The significance of these lesions with respect to later disease is not determinable from the data at hand. It is thought possible that in the older lesions, especially the ossified ones several decades old, the parasites are dead. The reason is that in some of the lesions no budding forms were found and some had lost birefringence almost entirely, but this is only speculation.

Two illustrative cases will be given:

D. H. B. 21 No. 25,139 (Fig. 19A). This was a 45 year old Caldwell County farmer who recently was in St. Luke's Hospital in Kansas City for diarrhea, fever, cough, fatigue, loss of weight which had taken place over a three month period. An x-ray film revealed an infiltrate in the right apex with a diagnosis of probable tuberculosis. He was advised to enter the Missouri State Sanatorium.

His past history revealed that he had appendectomy in 1935, tonsillectomy in 1937, and stomach resection for ulcer in 1949. Laboratory examination revealed one skin test weakly positive for histoplasmosis. Many were negative. There was one weakly positive complement fixation test for histoplasmosis with several negatives. The tuberculin

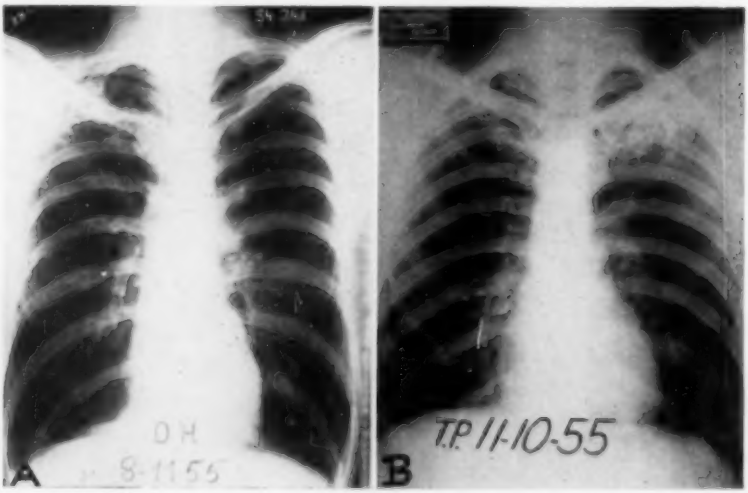


FIGURE 19 FIGURE 20

Figure 19: (A) Roentgenogram of D. H. B21, No. 25,139, taken on August 11, 1955, showing a fibroid and partly infiltrative lesion in right subapex.—*Figure 20:* (B) Roentgenogram of T. P. B23, No. 25,223, taken on November 10, 1955 showing a more inflammatory type of lesion in the left subapex.

test was entirely negative. Several cultures of the sputum were positive for H. capsulatum as well as positive on mouse inoculation. A culture of the lung tissue was also positive for H. capsulatum.

On December 13, 1955, right upper lobectomy was performed by Dr. Polk and his assistants. The pathological findings were as follows: The specimen was that of the right upper lung lobe. The lobe was of a reddish-black appearance on the surface with many black outlines of lymphatics. On section, the appearance resembled somewhat that of a tuberculous process. Several cavities and many masses of caseous material were seen. The appearance resembled that of tuberculosis but the hue and arrangement of the caseation and the character of the caseation resembled that found in histoplasmosis. The largest cavity in the subapical region measured about 2½ x 3 cms. in diameter. There were several bands across this cavity. The cavity wall lining was slick and serous-like in appearance. It was covered by adhesions that extended out into the parietal pleura and covered an area of several centimeters over the dome of the lobe. The other cavities were smaller in size and did not have this bullous-like appearance. They were found in the subapical region and extended well down toward the base of the upper lobe. They ranged from 5 to 10 mm. in diameter. Most of them were multilocular. The walls of these cavities were about 2 mm. in thickness and had a dirty-gray granular appearance. There was a sort of dirty-gray thin pus that was contained in these cavities which did not resemble the pus ordinarily found in a tuberculous process. There were some infiltrative areas where the excavation of the cavity had not taken place. All together there were probably 8 to 10 different areas of cavity formation or of infiltration from this disease process. The lymph nodes did not reveal anything grossly. The bronchi seemed to be normal.

Microscopic examination of a number of sections revealed rather extensive chronic granulomatous involvement wherein there was seen much parenchymal replacement by varying sized lesions, some of which had a tubercle-like formation of fibrous elements and central multinucleated foreign body giant cell formation. Others presented an occasional small central area of necrosis and around which there was pronounced fibrous proliferation and a chronic inflammatory reaction of a mixed type. There were seen several irregular outlined lesions of caseonecrosis in which the lining elements were made up of compact fibrous tissue containing one to several multinucleated giant cells and relatively small numbers of reactive cells. In some sections there were also seen pneumonic involvement wherein the alveoli were filled with macrophages, some of which contain hemosiderin pigment, others cellular debris. In some of the giant cells there were seen asteroid structures, in others amorphous structures and occasionally some contained oval shaped, small, clear vacuole-like structures. The lesions did not appear to be typical of tuberculous involvement. Sections stained by the PAS stain revealed an occasional stained intracellular structure compatible with Histoplasma capsulatum. The diagnosis was chronic granulomatous pneumonitis with cavitation secondary to Histoplasma capsulatum. The supplementary report revealed that the G. M. S. stain identified many lavender stained bodies that were 3-5 microns in size and were compatible with H. capsulatum. Final diagnosis: Pulmonary histoplasmosis.

Comment: It is highly probable that three or four of the old calcific lesions were part of an old "primary complex," as Straub and Schwarz[15] have reported, but since we were not able to examine all of the lymph nodes it was not possible to prove this suspicion. Several cases of definite primary complex of only a few years' duration will be reported later.

In the more caseous lesions, even though they are well encapsulated, it is thought that most of the parasites are living, largely because of budding forms present. In fact, some evidence seems to point to the fact that they survive as long or much longer than do tubercle bacilli in a similar type of lesion. Thus the carrier state may be prolonged indefinitely, even if only a few infections ever develop into clinically active disease. The yeast bodies are found in great abundance in caseation in contradistinction to tubercle bacilli.

Some of these lesions may be similar in nature to the large encapsulated circumscribed lesions, except that the defensive balance operated sooner and produced a heavy impervious capsule that kept the lesion small and the parasites within bounds.

The fourth group of cases consists of chronic pneumonitis. These have been fairly well described by Binford and others, and it would appear that the development of these lesions is rather constant. Probably it would be well first to describe the appearance of these lesions from the standpoint of gross pathology. The condition existed in at least five of the cases that we studied and the pneumonitis extended into the fairly normal lung tissue beneath the cavity usually from 2 to 3 cm. The appearance and the feel of the lesion grossly was similar to a tuberculous caseous pneumonia. Microscopically, however, there was a considerable difference between this and an acute tuberculous lesion. Finding this type of lesion in a patient that has been treated for a long time with anti-tuberculosis drugs is strong evidence in favor of histoplasmosis. There was considerable variation in the pattern, but most of the lesion is granulomatous with epithelioid cell proliferation and varying numbers of Langhan's giant cells. (Figs. 23 and 24). There may also be areas of early organizing subacute fibrinous pneumonia with varying numbers of histiocytes present. Then around the margins may be purely histiocytic infiltration, some of which may contain

FIG. 21

FIG. 23

FIG. 22

FIG. 24

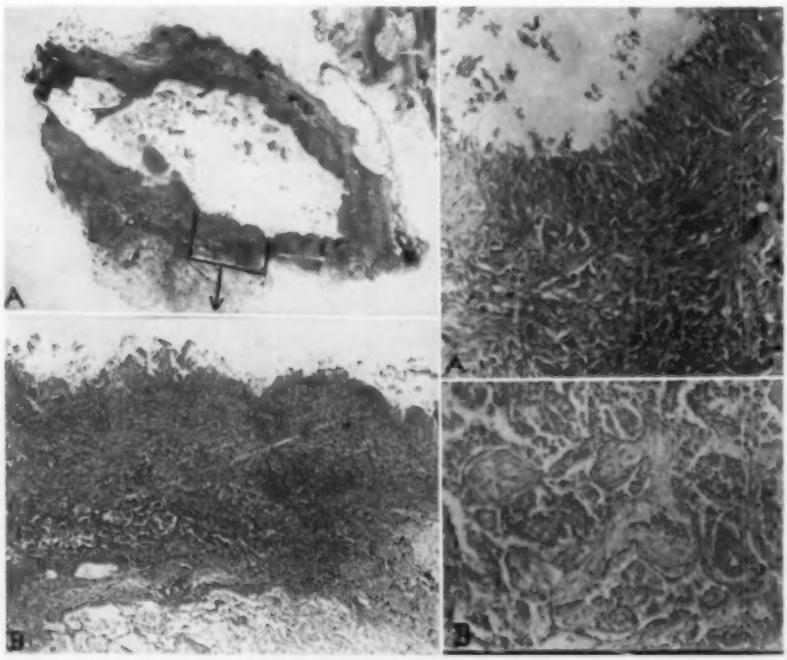


Figure 21: (A) A low power view of two of the fibroid cavities shown in Fig. 17. H. & E. × 6.—*Figure 22:* (B) A higher magnification of wall of cavity marked off in Fig. 19. H. & E. × 36.—*Figure 23:* (A) A still higher magnification of wall of cavity of Fig. 19. Note palisade arrangement of cells. H. & E. × 160.—*Figure 24:* (B) An area of chronic pneumonia in lung tissue showing alveoli packed with organizing fibrous exudate, with alveolar cells and macrophages. H. & E. × 132.

parasites, but as a rule the parasites were very rare in the granulomatous parts of the lesion.

T. P. B. 23, No. 25,223 (x-ray shown in Fig. 19B), was a 49 year old Ozark County farmer who had for 12 months complained of malaise, weakness and inability to cope with his duties. A Mobile Unit found the lesion in the upper lobe of the left lung and he was sent to this hospital.

The skin test was found strongly positive for histoplasmosis and negative for tuberculosis. Complement fixation for histoplasmosis was negative. One sputum specimen was positive on culture and produced disease in a mouse as reported by Dr. Furcolow. All other tests were negative including culture of lung tissue and lymph nodes. Since the lesion was isolated in the left upper lobe the conference decided upon excisional surgery because of the possibility of cancer.

On November 15, 1955, therefore, Dr. Polk and his assistants did a lobectomy of the left upper and an excision of hilar nodes (Figs. 25, 26 and 27).

Pathological findings of the upper lobe of the left lung and hilar nodes. Gross: The disease was rather extensive but there was much good lung tissue remaining, especially in the lingula and in the middle portion. In the apex there was a great deal of caseous material and there were two or three small cavities, one of which measured 2½ cm. in diameter with grayish, rather caseous walls, 2 to 3 mm. in thickness. There were two or three areas of what appeared like caseous pneumonia adjacent to these cavities. In this pneumonic aren were several soft, rather dry caseous "tubercles" measuring 2 to 5 mm. in diameter. There were two to three cavities that measured 1 to 2 cm. in the midportion of the lobe. The only abnormal feature in the lingula was that it

FIGURE 25 FIGURE 26 FIGURE 28

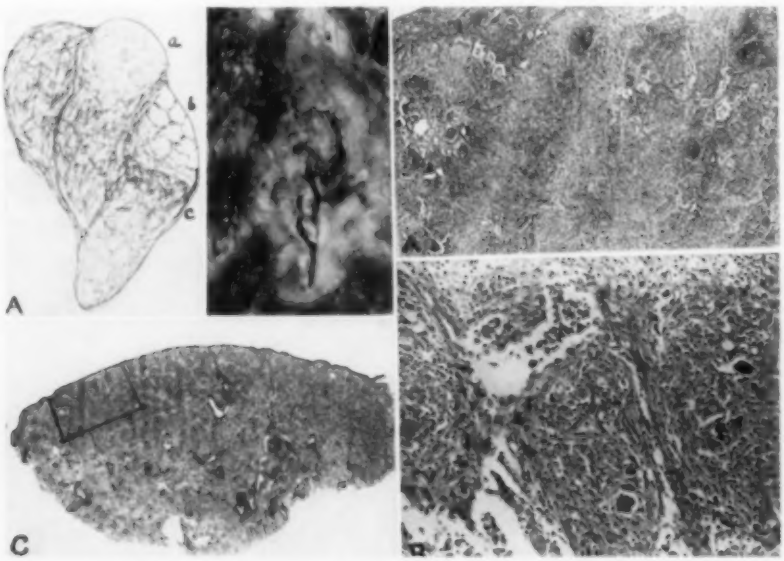


FIGURE 27 FIGURE 29

Figure 25: (A) A sketch of resected upper lobe of T. P. B23, No. 25,223, purporting to show the cystic protrusion at "a," the chronic pneumonia at "b," and the atelectasis at "c."—*Figure 26:* (B) A slightly enlarged caseous focus from the consolidated region below the cystic cavity with early cavity formation. H. & E. × 4.5—*Figure 27:* (C) A low power photo of section of the chronic pneumonitis at "b" in Fig. 23. H. & E. × 4.5.—*Figure 28:* (A) A higher magnification of area marked off in Fig. 25. H. & E. × 20.—*Figure 29:* (B) A still higher magnification of an area of the chronic pneumonitis. Note the imperfect giant cells, fibroblasts, fibrosis, macrophages, and the few lymphocytes with no polymorphs. H. & E. × 140.

had much hypostatic congestion. The lymph nodes near the hilum were not particularly enlarged and contained black pigment. The bronchi were practically normal.

Microscopic examination showed a chronic granulomatous inflammatory reaction characterized by presence of areas of caseonecrosis as well as areas of cavity formation and also small areas of pneumonic inflammatory reaction. The cavitations and the areas of caseonecrosis were bordered by fibroblasts arranged more or less in a picket-fence formation with an occasional mononucleated cell of irregular outline. Adjacent and also in other more distant areas there was a pneumonic involvement wherein the alveoli were filled with numerous histiocytes mostly of fibroblastic type. Occasionally these showed an early central caseation. A few of the giant cells contained asteroid-like structures and examination under high power and oil immersion showed the presence of only one small rounded intracellular structure which resembled a yeast body. Preliminary diagnosis was histoplasmosis.

A re-examination of the slides stained by PAS stain revealed many phagocytic monocytes that contained bodies appearing like Histoplasma capsulatum. The G. M. S. stain revealed many typical yeast-like bodies, some in the cavity walls showing budding, as well as a great many in the encapsulated areas. These were of the same size and character of Histoplasma capsulatum. Final diagnosis—Histoplasmosis.

The fifth group, the ulcerative type, may be divided into the caseo-ulcerative and fibroid. The former were cavities developing in caseous areas similar in most respects to the caseous nodular lesion, except that they were larger and it resulted in a central cavity which communicated with a bronchus. (See Fig. 26.) Parasites may be found in the walls of most of these lesions, but they were not as numerous as they were in the encapsulated lesions. In the other type of ulcerative lesion, the fibroid type, the cavity may be of a cystic nature with a relatively smooth wall and a thin fibrous cyst-like bulla that extends above the surface of the lung. Another form was found to have a thin wall as a result of a rapid destruction of lung tissue similar to that of a progressive tuberculosis. Again there were cases

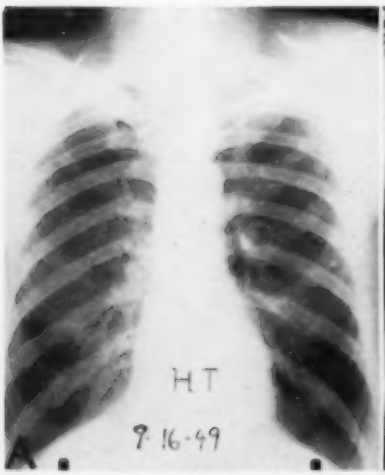


FIGURE 30

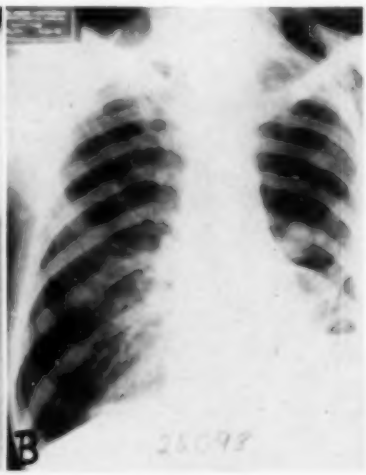


FIGURE 31

Figure 30: (A) Roentgenogram of H. T., B28, No. 26,098, taken on September 16, 1949 showing a fibroid apical lesion in the left apex and a few nodules below. It was called a moderately advanced tuberculosis with an apical cavity.—*Figure 31:* (B) Same case taken on August 31, 1956 showing what was thought to be a pneumothorax because of the fibrin body showing. Instead it was found to be a completely destroyed lung.

where there was a dense fibroid wall as much as two centimeters in thickness, simulating chronic fibroid tuberculosis. In practically all but the recent ulcerative lesions, parasites were rather scarce in the cavity walls and difficult to culture, but were found in great numbers in the adjacent encapsulated lesions, either in the pulmonary tissue or in the lymph nodes. An illustration of a progressive ulcerative lesion is afforded by the next case.

FIG. 32

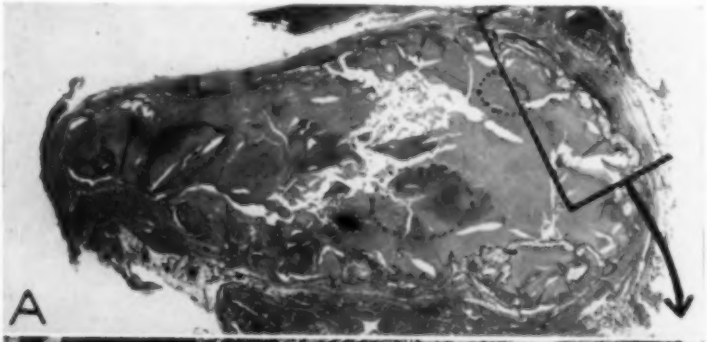


FIG. 33

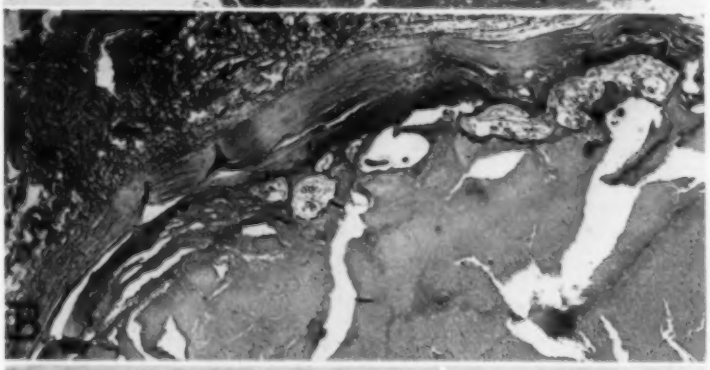


FIG. 34

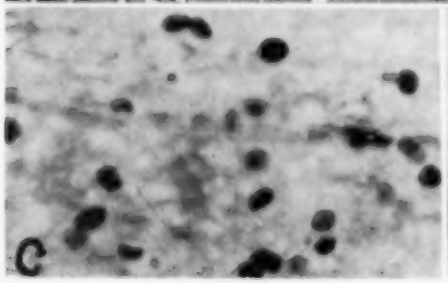


FIG. 35

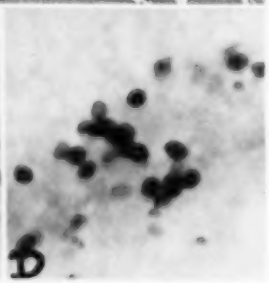


Figure 32: (A) A low power view of dense ossified parenchymal lesion shown in Fig. 31. There was also a lymph node lesion left behind, perhaps the lymph node component of an old primary. Small dots encircle several areas in which yeast bodies were found. H. & E. × 4.5.—*Figure 33:* (B) An enlarged area outlined in black ink. Note the bone and marrow.—*Figure 34:* (C) Microscopic view of yeast bodies found in area outlined by dots in Fig. 32. G. M. S. stain × 3200.—*Figure 35:* (D) Another field outlined by the dots in Fig. 32. G. M. S. stain × 3200.

H. T. B. 28, No. 26,098. This was a 55 year old widowed Mississippi County laborer. He gave a history of having a 12 year coal mining experience in Kentucky 25 years ago. Since then he has worked in timber and saw-milling.

In the past 20 years he had three bouts of "pneumonia" and several gastro-intestinal attacks thought to be due to gall stones and for which he was operated on in 1935. More recently he had severe chest pains with productive cough, loss of weight, chills, nightsweats, streaked sputum and bouts of fever. An x-ray film showed a spot on the left upper lung field. By 1947 he had a large hemorrhage which confined him to bed for six weeks. Tubercle bacilli were never found. An x-ray film in 1949 was read as "moderately advanced tuberculosis with a well defined cavity." Again on January 14, 1950: "Right: negative except for calcifications in the hilum. Left: Diffuse haziness in the apex with ill defined mottling in the second interspace." This was after the patient had been admitted to our hospital on January 13, 1950. He was discharged May 5, 1950 as an arrested case.

As a checkup an x-ray film taken August 11, 1953 was reported as follows: "Right: no change. Left: The areas of rarefaction in the upper lobe of the left lung were larger and so were the emphysematous blebs seen in the lower lobe." On March 19, 1955: "Right remains clear. Left: Has been completely destroyed since the previous film. The entire upper third was occupied by a giant bleb or cyst and multiple large cysts occupy the remainder of the lung field."

On July 13, 1956 he was re-admitted to the hospital and the x-ray film reading was reported as follows: "The left lung was thought to be collapsed with effusion and empyema. In the right apex there was an area of rarefaction considered to be a small cavity." He had "heart trouble" with edema of the extremities. He was treated with digitalis for the heart trouble and was unable to work since then. He was advised to re-enter the sanatorium but refused, gradually becoming worse until he became bedfast. He developed pain in the chest with continuation of the symptoms and had two rather large hemorrhages over the last two years before the second admission on July 13, 1956.

The laboratory examinations have been uniformly negative for acid fast bacilli although there was abundant sputum and there were a large number of examinations. One sputum culture was positive in our laboratory for H. capsulatum. Three successive gastric lavages were also positive for H. capsulatum as was one fluid from the chest cavity. All subsequent examinations for H. capsulatum were negative or the cultures were over-grown with bacteria and Geotrichum. The complement fixation test throughout this patient's second stay in the hospital was rather strongly positive, going as high as 1:64 dilution. The tuberculin skin test was weakly positive. There were no other positive findings, including the subsequent examination of the resected specimen for yeast by both Dr. Furcolow and our own laboratory.

After due consideration in the Staff Conference pneumonectomy was decided upon and was carried out by Dr. Polk and his assistants on September 19, 1956. The pathologic findings were as follows: The gross specimen representing the whole left lung was made up of an extensive cavity that involved the greater part of the organ. The over-all dimensions of this specimen, including the decortication of the pleura, was about 20 cms. from apex to base and about 15 cm. wide and 10 cm. in the third dimension. It was difficult to estimate the dimensions of the cavity but it was a centimeter or two less each way than that given for the over-all measurements. There were numerous blood vessels that crossed the cavity from the apex all the way to the base. On dissecting down the larger bronchi, over half of them were found to terminate in this huge cavity. The average bronchus was about 4-5 mm. in diameter when it entered the cavity and there was a smooth opening of the bronchus at the point of entry. This opening was rather flaccid and tended to make a valve-like structure in the cavity and helped to keep it distended. Around the trunks of the main bronchi were areas of solid black atelectatic lung tissue.

Microscopic examination showed very extensive alteration of the normal pulmonary tissue by chronic inflammatory process in which there was much fibrous proliferation with replacement of pulmonary tissue. In areas bordering the grossly described cavitation, portions presented granulation tissue formation overlying an area of hyalin-like material. More peripherally there was fibrous proliferation with secondary hyalin changes. A portion of the cavitation presented a proliferation of the bronchial epithelial mucosa and occasionally this presented a metaplasia into the squamous cell type of epithelial membrane. In one section there was an exudative lesion in which there were some neutrophils and mononuclear macrophages many of which contained ingested cellular debris and in a few there were seen intracellular inclusion structures which are round and had a capsular halo around them. PAS stained tissue showed within this lesion several stained round structures with a clear halo around them which morphologically were compatible and certainly very suggestive of Histoplasma capsulatum. A section of several lymph nodes showed the architecture to be essentially

intact. The lymphoid follicles presented active normal centers. In one there were a number of histiocytes containing anthracotic pigment. No granulomatous inflammatory lesions were seen. Diagnosis: Left pneumonectomy showing chronic granulomatous pneumonitis with giant cavitation due to Histoplasma capsulatum.

After a stormy postoperative period he expired September 29, 1956. All organs, both gross and microscopic, were not greatly abnormal. Only the anatomic diagnosis will be needed for the purpose:

(1) Missing left lung—status postpneumonectomy.

(2) Chronic granulomatous inflammation of right lung, probably histoplasmosis; although no parasites were found.

(3) Atelectasis of right middle and lower lobes.

As with the other specimens, a re-examination of the material of this case was performed and a search for encapsulated and calcified lesions was made by very carefully sectioning every part of the lung specimens. The oldest calcified lesions were heavily encapsulated with fibrous and ossified tissue and there were many erosions around the border and some extended into the centers of the lesion. The open spaces left were filled with bone marrow surrounded by thin marginal strips of bone.

The G. M. S. stain revealed a large number of yeast bodies in several pockets within the calcified center (see Figs. 32-35 incl.). There were several accumulations of very small spore-like bodies in some places that appeared to be the beginning of the evolution of yeast bodies. Some of the larger spore-like bodies were birefringent. The smaller ones, less than one micron in diameter, only showed as a bright to orange point of light.

A few parasites were found in the wall of the cavity but they would have been missed had not the others been found in the calcified lesions.

Final diagnosis: Fibro-calcareous and ulcerative histoplasmosis.

Part II of this paper will appear in the September issue of Diseases of the Chest.

The Place of Steroids in Pulmonary Disease*

HARRY SHUBIN, M.D., F.C.C.P., ROBERT LAMBERT, M.D., F.C.C.P.,
CHARLES A. HEIKEN, M.D., F.C.C.P. and SAN SINGHAPHAKDI, M.D.
Philadelphia, Pennsylvania

This presentation will confine itself to the use of the steroids and their relationships, bad and good, to tuberculosis.

Although the clinical significance of the adrenal glands was first reported by Addison in 1855, comparatively little was known of its physiology until Selye showed its relationship to the "stress mechanism." Further studies by Hench, et, al., proved clinically the relationship of cortisone in inflammatory and allergic reactions.

Even at present, the corticosteroid preparations are clearly labeled as being contra-indicated in patients with active tuberculosis. This is due to the adverse affects first noted in early animal experiments[1-3] and in humans in whom cortisone caused an exacerbation of a previously unknown or quiescent tuberculosis.

Reports in the literature recently by various investigators[4-9] tend to show that the corticosteroids can be given safely with occasional dramatic results in active tuberculosis as long as anti-tuberculous therapy is being simultaneously administered. This is especially true in fulminating tuberculosis such as miliary and tuberculous meningitis.

This paper, therefore, will seem paradoxical, for it will tend to condemn a treatment where it has been previously advocated and advocate a treatment where it has previously been condemned.

Following the excellent results obtained in the treatment of rheumatoid arthritis,[10] bronchial asthma, inflammatory and allergic dermatitis, and eye conditions, its use has expanded to rheumatic fever, nephrosis, lupus erythematosis and other collagen diseases, blood dyscrasias, etc.

The first portion of this presentation will discuss cases of reactivated tuberculosis seen by the authors in patients receiving the corticosteroids for a variety of conditions. The reasons for reactivation and possible methods of prevention will also be discussed.

The second portion will review the results obtained by the use of steroids in patients with acute and chronic tuberculosis, who also were receiving antituberculous therapy.

While it may be true that the number of reactivated tuberculosis cases is comparatively small in proportion to the general usage of the steroids, nevertheless they are being seen with increased frequency by chest specialists[11] and warrant a flag of caution to our colleagues in other fields of medicine. Chart 1.

The following cases illustrate typical reactivation:

---

*Philadelphia General Hospital, Northern Division, and Rush Hospital.

CHART 1

ACTIVE TUBERCULOSIS BY DISEASE TREATED WITH STEROIDS*

Total Patients	38
Rheumatoid Arthritis	11
Bronchial Asthma	10
Boeck's Sarcoid	5
Periarteritis Nodosa	1
Lupus Erthematosis	3
Dermatitis—Allergic	4
Addison's Disease	1
Ocular Diseases (Uveitis etc.)	2
Polycythemia Vera	1

*Not one case covered by antituberculosis drugs.

D. K.—This 33 year old, white, nurse was first seen in 1950 with lesions in the left hilar region and right mid-lung field. During the next three years, this bilateral granulomatous type lesion gradually progressed to involve both mid-lung fields. She was completely studied at the University of Pennsylvania and bacteriological studies were negative. The tuberculin test, however, was positive. She continued to work until 1953, when she went to a hospital in Texas. While there, her condition was diagnosed as sarcoidosis and cortisone was administered.

At the end of one month, she returned to Philadelphia and because of productive cough and fever, she was readmitted for check-up. X-ray film revealed giant cavity in the right mid-lung field. Sputum at this time was positive for tubercle bacilli.

She is still being treated for tuberculosis but is now on an out-patient basis after three years in the hospital (Figure 1).

R. H.—40 years, colored, man. Had his first x-ray film taken in April 1955 which revealed large thin-walled bullae in both upper lobes with fibrosis extending from the hilum in both mid-lung fields. Tuberculin tests negative on all strengths; repeated sputum negative for acid fast bacilli. Scalene node biopsy was reported positive for sarcoidosis. He was placed on cortisone for one month without antituberculous coverage.

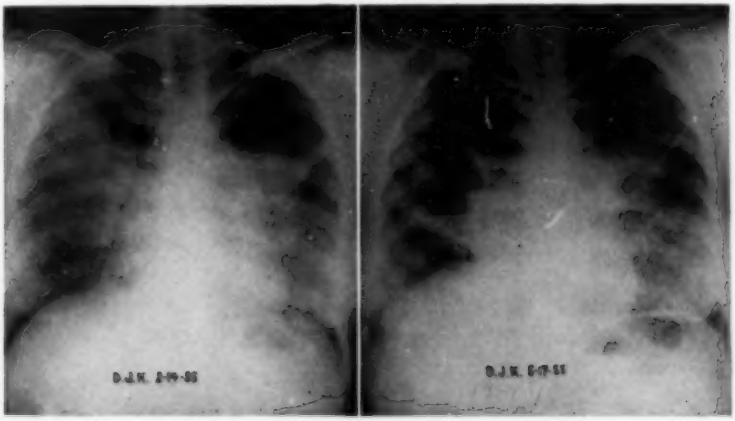


FIGURE 1

Two months later, while working at a steel mill, he had hemoptysis and was hospitalized where x-ray films revealed exudative type infiltration involving both lower lung fields. Sputum at this time was highly positive for tubercle bacilli.

He was then sent to Rush Hospital and started on streptomycin and INH. He has improved on this regime, although moderate cor pulmonae has developed. While the etiology of sarcoid has not been definitely proved, we feel these patients should not have steroid therapy without antituberculous drugs (Figure 2).

S. P.—59 years, white, man, was admitted to Temple University Hospital in July 1954. His past history revealed disseminated lupus erythematosis for one year, during which he received 100 mgm. cortisone daily. On admission, he was semi-stuporous, had left hemi paresis, and x-ray films showed far advanced exudative pulmonary disease. Tubercle bacilli were found in his sputum. He received streptomycin, INH and PAS; cortisone was discontinued and ACTH 20 U daily was given for two months. He was transferred to Eagleville and Potassium Paba was started in September 1954, after stopping the ACTH, but continuing INH and streptomycin. This regime is still being continued and he has had no recurrence of lupus with apparently stable inactive tuberculosis, after being at home for one year (Figure 3).

L. H.—This 63 year old, colored, man, was admitted to Rush Hospital February 10, 1956 for evaluation of lesion of chest. He had been treated in the arthritis clinic of another hospital since June 1955. During this time he lost weight and developed cough. He had been well until June 1955 when he developed arthritis of middle finger of left hand followed by swelling of hand and wrist. Shortly thereafter, his knees became swollen and tender.

Chest x-ray films on February 16, 1956 showed moderately advanced reactivated fibrocaseous pulmonary tuberculosis of the right upper lobe. X-ray film of knees showed evidence of rheumatoid arthritis of right and left knee joints. His erythrocyte sedimentation rate was 59 mm in 60 minutes. Blood serology was reactive in Kolmer and VDRL. Sputum positive for tubercle bacilli. Aspirated fluid from the knee was negative on smear and culture for acid fast bacilli.

Therapy was instituted with streptomycin and PAS and orthopedic care given to his knees. Duracillin was given, 600,000 units daily, for 10 days for reactive serology. He showed clinical improvement became afebrile, and slightly gained weight. This indicates the danger of using steroids in arthritis without preliminary and follow-up chest x-ray films for pulmonary pathology (Figure 4).

W. C.—was admitted to Rush Hospital December 4, 1956 with a diagnosis of bronchial asthma and possible pulmonary tuberculosis. Past history was positive for syphilis, for which he received treatment with the last serology report being negative a month prior to this admission. Before being hospitalized at Rush, he was in another hospital for asthmatic attacks and had a history of 20 lb. weight loss. During that hospitalization he was told that he had pneumonia. He developed indigestion and bloody stools but a gastrointestinal series was negative. However, he improved on an ulcer regime. While at Chester County Hospital, he had received cortisone for resistant asthma. He was consistently negative for acid fast bacilli while at Chester County Hospital. However, at Rush Hospital, sputum on smear was positive

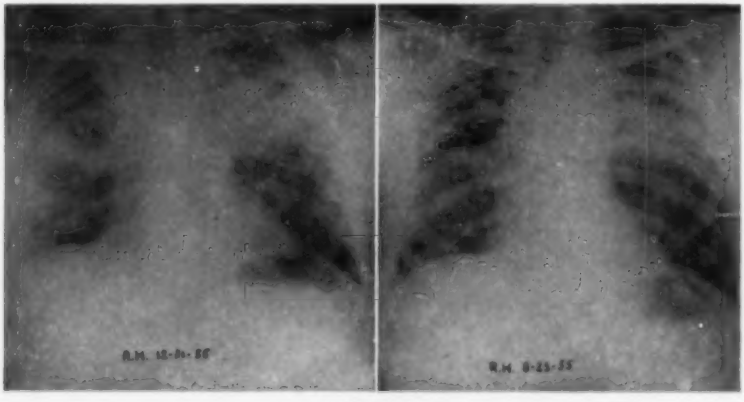


FIGURE 2

CHART 2A
THE USE OF STEROIDS IN TUBERCULOSIS WITH ANTITUBERCULOUS THERAPY

Acute Tuberculosis		33 Patients	
Miliary	12	12 excellent	
Meningeal	11	8 excellent	
		3 deceased	1 encephalitis 1 within 72 hrs. 1 staph-pneumonia
Pneumonic	8	7 excellent 1 deceased (within 24 hrs.)	
Lymphatic	2	2 excellent	

on three occasions. He was then placed on streptomycin and INH. X-ray films of the chest revealed evidence of caseous pneumonic disease of the left upper lobe on December 5, 1956. The last film on February 8, 1957 showed improvement in the pulmonary tuberculosis with residual evidence of cavitation, with positive sputum.

This patient illustrates two complications of steroid therapy; that is, the reactivation of pulmonary tuberculosis and exacerbation of gastric ulcer with possible gastrointestinal hemorrhage (Figure 5).

The main reasons for reactivated tuberculosis in this series were:

1) Failure to investigate the possibility of latent or inactive tuberculosis.

2) Failure to administer anti-tuberculous drugs with the steroids.

3) Excessive dosage and prolonged administration. It is easy to understand how complications develop from excessive dosage when we consider the amount of secretion of ACTH[12-13] from the anterior pituitary does not exceed one unit daily while the normal daily secretion of hydrocortisone from the adrenal cortex varies between 12 and 20 mgm in 24 hours.

Most steroid therapy is given in doses far in excess of that normally produced or needed by the body and generally when administered for periods longer than 10 days may lead to hypercortonism and suppression of the adrenal glands.

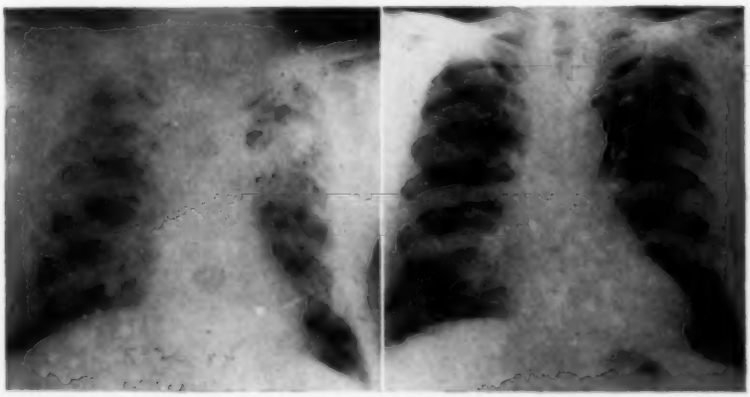


FIGURE 3

While the newer, more powerful analogues of cortisone—that is, (prednisone and prednisolone) are popular because of fewer side effects, they are equally as dangerous in producing complications of overdosage, especially since they are often administered in the presence of normally functioning adrenals.

Even more alarming is the recent tendency to combine prednisone in doses of from 1 to 2 mgm. with analgesics and antihistamines. Although this amount might appear to be inocuous, two of these tablets taken in the recommended dosage four times daily is in excess of the normal daily requirement of the body. This problem would be magnified if such compounds ever became available without prescription.

As a result of these findings, it is recommended that the following basic principles be considered:

1) Administer the minimal maintenance dose necessary to obtain desired clinical results.

2) Tuberculin test and x-ray film of the chest of all patients before starting therapy.

3) If suspicious of latent or inactive tuberculosis, administer simultaneous anti-tuberculous therapy.

4) After steroid therapy is discontinued, the patient's reaction to stress is diminished for at least the next six months. The readministrations of steroids at times of stress, such as surgery or infections, is not only necessary but life-saving.

The interest of the authors in the simultaneous use of steroids and antituberculous therapy in active tuberculosis was aroused in 1954. In spite of the many good results with chemotherapy in tuberculosis, there were still a group of patients who had received all forms of therapy without clinical or x-ray improvement. The possibility of adrenal insufficiency as a factor in the poor response was considered, is confirmed

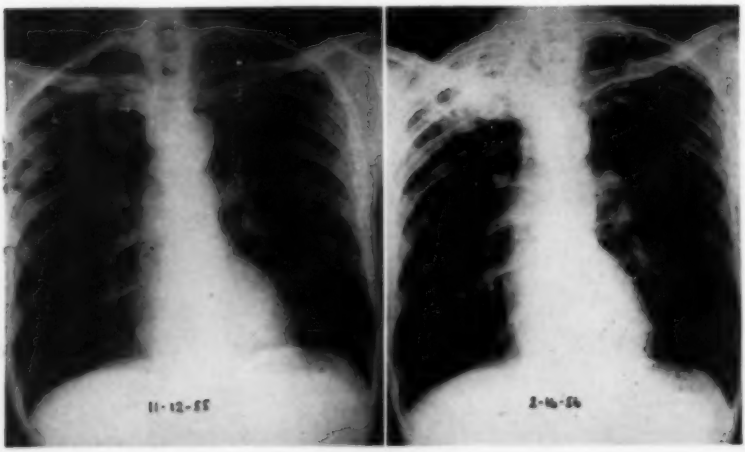


FIGURE 4

CHART 2B

Chronic Tuberculosis		60 Patients
Terminal type	11	8 survived 3 deceased (within one week)
Allergic drug reaction	14	7 successful 6 successful—with surgery 1 deceased (within 24 hours of surgery—"shock syndrome")
Active cases no longer responding to drugs	35	24 improved 11 unchanged

by the low 24 hour 17 Ketosteroid output. Since it has been shown that infections such as tuberculosis produce acute stress early in fulminating lesions and chronic stress in the prolonged form of disease. Resistance of the host to infection is dependent upon the reaction of the hypothalamus-pituitary-adrenal axis. It is fortunate that most tuberculous patients with normally functioning adrenals adapt themselves well to this stress. This study indicates that the steroids should be used in those patients whose adrenals have become exhausted and they do not react favorably to the stress of disease. Therefore, the first studies were in patients with poor prognoses from acute miliary or meningeal tuberculosis. As a result of the favorable response in the original terminal patients, the use of steroids was gradually expanded to include the more chronic forms of tuberculosis which were not responding to combined anti-tuberculous therapy, and to those showing allergic reactions to anti-tuberculosis drugs.

Prednisolone (Sterane) was given to 33 acute and 60 chronic cases as shown on the chart "The Use of Steroids in Tuberculosis *With* Anti-tuberculous Drugs" Chart 2. The following cases are typical of results in acute forms of tuberculosis:

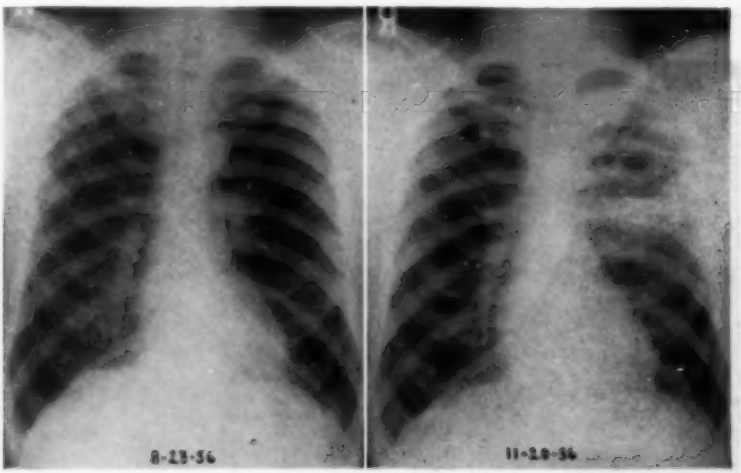


FIGURE 5

A. M.—This 41 year, colored, man, was admitted to Philadelphia General Hospital, Brockley Division, July 1954, toxic with left pleural effusion and x-ray film evidence of miliary tuberculosis. He did not react to the second dose of PPD. Streptomycin, INH and PAS, were administered but after two months, his clinical condition was worse, with temperature 103°F. X-ray films showed spreading disease and he was practically moribund. Pleural and urine cultures were reported positive for acid fast bacilli. Cortisone was started, 200 mgm daily plus the three antituberculous drugs, and gradually reduced to 25 mgm daily in a month. After one month, there was marked x-ray film clearing, he became afebrile and cortisone was discontinued. He then noted to the first dose 2 PPD. He remained in the hospital on triple drug therapy for six more months, when he was asymptomatic and the chest x-ray film appeared clear. He has been followed as an out-patient, and still maintains good health.

O. B.—This 15 year old, colored, boy was, admitted to Women's Medical College Hospital with cough, weight loss, fever and x-ray film evidence of miliary tuberculosis. Although there was no symptom of meningeal irritation, a spinal tap was done. It was negative for cells but showed slight increase in protein and decrease sugar. Streptomycin, INH and PAS were started on the day of admission. Meningeal irritation developed 36 hours after admission and repeat tap showed 275 cells, predominantly lymphocytes, increased protein and decrease sugar compared with previous tap. Prednisolone, 60 mgm daily was started with prompt reduction in temperature. Within three days all signs of meningeal irritation had disappeared. The prednisolone was gradually reduced by 2.5 mgm a day and finally discontinued after five weeks. Three weeks later x-ray film showed marked clearing of miliary infiltration.

He continued to improve clinically and because of the marked clearing of the x-ray film, this case was considered by some doctors to have sarcoidosis instead of tuberculosis. However, after three weeks, the culture from the spinal tap and sputum examinations revealed acid fast bacilli.

He was followed for six months after cessation of therapy with prednisolone and discharged with apparently clear lungs, inactive disease and negative spinal fluid. The triple anti-tuberculous therapy is being continued (Figure 6).

The following illustrate results in chronic forms of tuberculosis:

M. B., was admitted to Rush Hospital June 21, 1956, acutely ill. Physical examination was difficult because of the condition. Blood pressure 110/80. There were moist rales, bilaterally, anteriorly and posteriorly. His temperature was 104° F. on admission.

Hemoglobin was 10.5 Gm., and there was a faint trace of albumen and occasional white cells in the urine. Serology was non-reactive; fasting blood sugar was 80 mgm., BUN was 5.0 mgm. and 17 Ketosteroids were 4.3 mgm. in 24 hour urine specimen. Sputum was positive and x-ray film revealed bilateral diffuse fibrotic and caseous pneumonic excavative process bilaterally, having the appearance of tuberculosis with

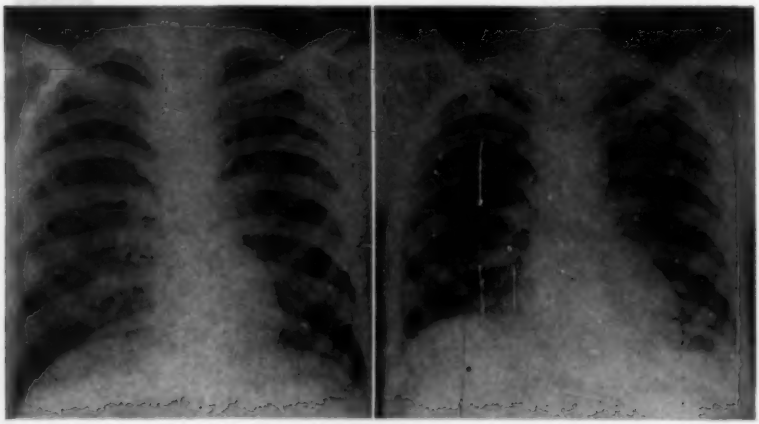


FIGURE 6

associated pneumoconiosis to be excluded. He remained toxic, with temperature about 101° F.

Chemotherapy was started June 23rd with distrycin and PAS. On August 14th INH was added and the Sterane routine on September 25th. He became afebrile by October fifth. His cough had decreased and he had gained 23 lb. since admission.

X-ray film on October 31st showed marked improvement in the tuberculosis, which was apparently superimposed upon pneumoconiosis. He is continuing treatment at Veterans Administration Hospital, East Orange, New Jersey (Figure 7).

J. A. D. This 47 year old white man was admitted to Rush Hospital May 16, 1956. There was marked weight loss, fever and malnutrition, blood pressure 95/70. A diagnosis of far advanced pulmonary tuberculosis was made in addition to cirrhosis of the liver, peripheral neuritis and malnutrition. He was overly alert, active and talking incoherently. His sputum was positive for tubercle bacilli. Fasting blood sugar 105 and BUN 4.7 mgm. Hematocrit 25 per cent, 17 Ketosteroid 24 hour urine 3.3 mgm., urine showed trace of albumen, white blood cells two to four per high power field with occasional red blood cell, moderate number hyaline casts. Hemoglobin 8.5 Gm., and Wassermann negative.

Chest x-ray film on admission revealed far advanced bilateral fibrocaseous and caseous pneumonic pulmonary disease with multiple areas of cavitation. An electrocardiogram showed some evidence of cardiac abnormality, probably electrolyte imbalance. There was a petechial rash on his hands, wrist and face. The liver was felt four fingers below costal cage and there was four plus pitting edema of feet.

He was started on INH and streptomycin, high vitamin diet and sedatives. He had two transfusions a few days after admission, receiving 500 cc. of whole blood each time. He was also started on the steroid routine. In September, he began to develop epigastric pain and since it was felt there might be an ulcer, he was put on ulcer regime. He began to improve clinically and gained weight to 130 lb. Because of recurrent spiking of temperature, systemic infection was thought to be present. Gall bladder films were negative. By October, cortisone was slowly reduced and he received in addition, ACTH. Blood pressure was now 120/78 and the sputum was negative by smear and culture. Ketosteroids 3.1 mgm. His urine was essentially normal. X-ray films showed improvement but a major lesion was still demonstrated in the upper lobe of the left lung.

The steroids apparently saved him from progressive, probably fatal condition, and now enables us to control his disease (Figure 8).

In exerting its anti-inflammatory effect, the steroids reduce toxicity and fever, appetite improves with weight gain, resulting in improved morale. The reduction of toxicity is illustrated by the following case:

W. M. S. This 41 year old colored housewife was admitted to Philadelphia General Hospital, Northern Division, on July 10, 1956 with history of cough, productive sputum,

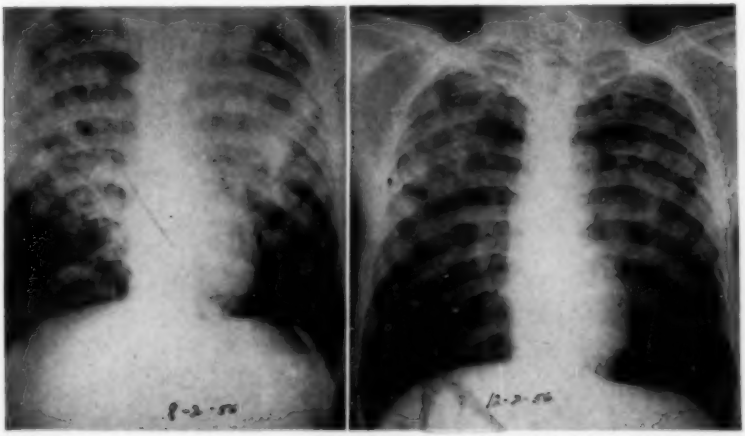


FIGURE 7

dyspnea and sweats for four months. She also has chest pain, anorexia and weight loss from 115 to 86 pounds. X-ray film showed extensive pulmonary lesions with large multiple areas of cavitation of the entire upper half of right lung. She also had disease in the left lung. Her sputum contained acid fast bacilli. She received triple drug therapy for three months with slight improvement. X-ray film showed no appreciable change, and she continued febrile.

Sterane regimen was started on October 1, 1956 and her temperature returned to normal. X-ray films on November 21 and December 31, 1956, February 1 and March 4, 1957, showed progressive improvement with marked clearing of the exudative shadows. After three months of treatment, she gained from 80 to 114 pounds and had persistently negative sputum.

The marked weight gain is shown by the next case:

E. D. This 55 year old colored man was admitted to Philadelphia General Hospital Northern Division, on December 27, 1956 with far-advanced bilateral active pulmonary tuberculosis. He was placed on Distrycin and PAS with poor results. He lost from 124 to 113 pounds in less than two months and became worse clinically. He raised more sputum which was consistently positive. His x-ray film appearance remained essentially unchanged. Sterane was started on February 9, 1957 and he gained to 140 pounds in two months. Although there is still little change in the x-ray film appearance, his sputum has been negative since March 20, 1957 and he feels much better. Because of this improvement, he can now be considered for other definite therapy.

Discussion and Conclusions

Any major discovery in medicine is accompanied by complications or side-effects, until its proper place in our armentarium is determined. The steroids are no exception. The original cortisone or hydrocortisone drugs produced electrolyte imbalance, sodium retention and subsequent fluid retention, etc., which is not seen with prednisone or prednisolone.

However, its beneficial effect in rheumatoid arthritis, asthma, collagen diseases, etc., is counteracted by the reactivation of latent or inactive tuberculosis. This has been observed in 38 patients of which five typical reactivations were discussed. The patient must be studied for evidence of pulmonary tuberculosis and if doubtful, give anti-tuberculosis drugs. Finally, use minimum dosage of steroids for short periods to obtain desired effects.

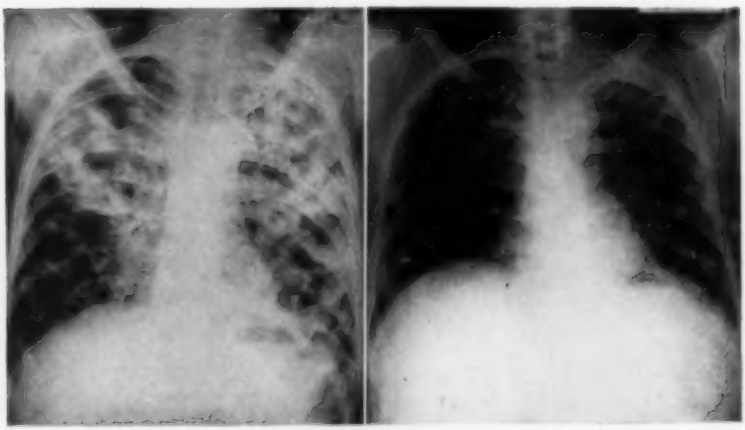


FIGURE 8

The results on 93 patients in this study further proves the value of steroids in the treatment of tuberculosis. Its effect may be life-saving in the acute, toxic forms; hastens desensitization and is beneficial in some patients with chronic tuberculosis. It is always effective chemotherapy.

What appeared a paradox in determining the place of steroids in pulmonary diseases, can now be properly evaluated by having complete studies of patient before and during treatment, and proper protective therapy against tuberculosis during steroid administration.

SUMMARY

This presentation attempted to determine the place of steroids in pulmonary diseases, especially tuberculosis. The beneficial effects of various steroids in rheumatoid arthritis, asthma, collagen diseases, etc., are well known. However, we reported 38 patients, who had reactivation of latent or inactive tuberculosis following such therapy. The physician must investigate the presence of tuberculosis, by skin test and x-ray films, and when in doubt, simultaneously administer anti-tuberculosis drugs. Only by using these drugs judiciously, that is, the minimum dosage for the shortest period necessary to obtain the desired effects, are complications diminished.

Paradoxically, the value of steroids in the treatment of tuberculosis has been established. From its life-saving action in 33 acute, toxic, miliary, meningeal, etc., to its stimulation effect in 60 chronic patients, either prolonging their lives, or hastening desensitization thus allowing more effective therapy. All of these patients received effective anti-tuberculosis chemotherapy during this study.

Acknowledgment: We wish to thank Doctors R. V. Cohen, L. Collins, H. Israel, R. Katzin, E. W. Marshall, R. Mayock and J. Schley for allowing us to use some of their patients in this study; and Doctors M. Carlozzi and K. Dumas of Chas. Pfizer & Co. for supplying the prednisolone and for their cooperation.

RESUMEN

Esta comunicación intenta determinar el lugar que ocupan los esteroides en el tratamiento de las enfermedades pulmonares y en particular en tuberculosis. Los benéficos efectos de los diversos esteroides en la artritis reumatoide, el asma, las enfermedades de la colágena, etc., son bien conocidos.

Sin embargo, relatamos el caso de 38 enfermos que han tenido una reactivación de tuberculosis latente o inactiva después de tal terapéutica. El médico debe investigar la presencia de tuberculosis por las reacciones cutáneas y las radiografías y en caso de duda administrar simultáneamente las drogas antituberculosas. Sólo usando estas drogas juiciosamente, esto es, con la dosificación mínima por el más corto período de tiempo necesario para obtener los efectos deseados, disminuyen las complicaciones.

Paradójicamente, el valor de los esteroides en el tratamiento de la tuberculosis se ha establecido.

Sus efectos van desde el que hace al salvar la vida de 33 casos de formas agudas, tóxicas, miliares y meníngeas, hasta el estimulante en 60 casos crónicos ya sea prolongando sus vidas o acelerando la desensibilización permitiendo así una terapéutica más efectiva. Todos estos enfermos recibieron quimioterapia antituberculosa efectiva durante este estudio.

RESUME

Cette communication tente de déterminer la place des stéroïdes dans les affections pulmonaires, et particulièrement la tuberculose. Les effets favorables des différents stéroïdes dans l'arthrite rhumatismale, l'asthme, les maladies du collagène, sont bien connus. Cependant, les auteurs ont rapporté l'observation de 38 malades, pour qui un tel traitement entraina une réactivation de tuberculose latente ou inactive. Le médecin devrait faire les investigations nécessaires pour reconnaitre la présence de tuberculose par tests cutanés et radiographies, et s'il y a un doute, administrer en même temps que le produit des médications antituberculeuses. Par le seul emploi judicieux de ces médications, c'est-à-dire en utilisant le dosage minimum pendant la période de temps la plus courte pour obtenir les effets désirés, on diminue les complications.

Paradoxalement, la valeur des stéroïdes dans le traitement de la tuberculose a été bien établie. Elle va de l'action salvatrice dans 33 cas aigus, toxiques, miliaires ou méningés, etc. . . . à l'effet stimulateur chez 60 malades chroniques, soit en prolongeant leur vie, ou en hâtant la désensibilisation et par conséquent en permettant une thérapeutique plus efficace. Tous ces malades reçurent une chimiothérapie antituberculeuse effective pendant cette étude.

ZUSAMMENFASSUNG

Diese Darstellung unternimmt den Versuch, den Platz der Steroide bei Lungenkrankheiten, besonders bei Tuberkulose zu bestimmen.

Die Heilwirkungen verschiedener Steroide bei rheumatischer Arthritis, Asthma, Bindegewebserkrankungen usw. sind wohl bekannt. Wir berichteten jedoch über 38 Patienten, bei denen eine Reaktivierung einer latenten oder inaktiven Tuberkulose einer solchen Behandlung folgte. Der Arzt muss auf das Vorliegen von Tuberkulose durch Hautproben und Röntgenaufnahmen untersuchen und in Zweifelsfällen gleichzeitig antituberkulöse Mittel verordnen. Nur durch vernünftigen Gebrauch dieser Mittel, d.h. die kleinste Dosis für die kürzest nötige Zeit zur Erlangung der gewünschten Effekte, setzt man die Komplikationen herab.

Im entgegengesetzten Sinn wurde sodann der Wert der Steroide bei der Behandlung der Tuberkulose bestimmt. Von ihrer lebensrettenden Wirkung bei 33 akuten, toxischen, miliaren, menigialen usw. Patienten bis zu ihrer stimulierenden Wirkung bei 60 chronisch Kranken entweder hinsichtlich einer Lebensverlängerung eder einer Beschleunigung der Desensibilisierung wird so eine wirksamere Therapie möglich. Alle diese Kranken erhielten eine wirksame antituberkulöse Chemotherapie während dieser Untersuchung.

REFERENCES

1 Lurie, M. B., Zappasodi, P., Dannenberg, A. M. and Schwarz, J. B.: "Constitutional Factors in Resistance to Infection. The Effect of Cortisone on the Pathogens of Tuberculosis," *Science*, 113:234, 1951.

2 Ebert, R. H.: "In Vivo Observation on the Effect of Cortisone on Experimental Tuberculosis Using the Rabbit Ear Chamber Technic," *Am. Rev. Tuberc.*, 65:64, 1952.

3 Karlson, A. G. and Gainer, J. H.: "Influence of Cortisone on Experimental Tuberculosis in Guinea Pigs," *Dis. Chest*, 20:469, 1951.

4 Chakravarty, S.: "The Place of ACTH and Cortisone in Therapy of Tuberculosis." In: Antibiotics Annual 1955-1956, New York, *Medical Encyclopedia, Inc.*, 1956, pp. 192-201.

5 Shubin, H. and Heiken, C. A.: "A Study of Effects of Steroids on Patients with Tuberculosis," Antibiotics Annual, 1956-1957, *Medical Encyclopedia, Inc.*, New York 1957, pp. 437-446.

6 Houghton, L. E.: "Combined Corticotrophic Therapy in Pulmonary Tuberculosis," *The Lancet*, —:595, 1954.

7 Crofton, J.: Southfield Hospital, Liberton, Edinburgh: Personal communication, October 1, 1956.

8 Handley, A. E.: "The Use of Corticosteroids in Combination with Isonicotinic Acid Hydrazide in the Treatment of Advanced Bilateral Progressive Cavitary Pulmonary Tuberculosis," *South African M. J.*, 30:605, 1956.

9 Favez, G. and Aguet, F.: "Hydrocortisone and Prednisone for Active Pulmonary Tuberculosis," *Schweiz. med. Wschr.*, 86:843, 1956.

10 Hollander, J. L.: *Comroe's Arthritis and Allied Conditions*, ed. 5, Philadelphia, Lea & Febiger, 1953, pp. 319-336.

11 Charpin, J. and Béranger, J.: "The Risk of Tuberculosis in Adrenal Cortex Therapy," *Presse méd.*, 64:1507, 1956.

12 Bethune, J. E., Ganong, W. F., Hume, D. M. and Nelson, D. H.: "Plasma Levels of ACTH in Normal Subjects and Addisonian Patients Following Corticosteroid Administration," presented at meeting, Endocrine Soc., Chicago, Ill., June 7-9, 1956, abstracted, *J. Clin. Endocrinol.*, 16:913, 1956.

13 Kern, R.: *Am. College Chest Physicians*, Post Graduate Course, Philadelphia, March, 1957.

Lobarspirometry*

I. Description of the Catheter and the Technique of Intubation

E. R. CLARKE, JR., M.D., C. J. MARTIN, M.D. and SERGEI POLITOFF
Seattle, Washington

Introduction

The ability to measure the function in anatomical divisions of the lung has not kept pace with the surgeon's competence in resecting smaller and smaller units. Knowledge concerning the relative function of small divisions has been derived from pre- and postoperative bronchospirometric measurements, since techniques for direct measurement have not been available until recently.[1-3]

In 1951, a spirometric catheter for the direct measurement of lobar function was designed in this laboratory. The first model was tested in 1953, and was improved upon as a result of subsequent experience. The purpose of this paper is to describe this catheter, to discuss the technique of intubation, and to indicate situations in which use of this catheter may be of particular value.

The Catheter

The catheter (Fig. 1A) is a three-lumen, soft latex-rubber tube 40 cm. long and from 1.1 cm. to 1.5 cm. in outside diameter. One channel extends the entire length of the catheter, and forms the airway to the lower lobe. A second channel parallels the first until, near the tip of the catheter, it turns away at 90° and forms the airway to the upper lobe. Each of the airways to the upper and lower lobes has an internal diameter of approximately 5.3 mm. The third channel, considerably shorter than the other two, is the airway to the contralateral lung, and has an internal diameter of approximately 6.5 mm.

The most distal balloon, when inflated, occludes the main stem and upper lobe bronchus, thereby functionally separating the lower and the upper lobe. The detail of this balloon is shown in Figure 1B. The proximal balloon occludes the trachea, and acting together with the distal balloon, isolates the contralateral lung.

Figure 1C illustrates the body of the catheter in cross-sectional diameter, and shows the relationship of the five lumina to one another and the means of assuring only minimal wastage of space. At the lower and upper ends of the catheter these triangular divisions become rounded, and continue as a tube.

At the tips of the upper- and lower lobe channels, two parallel lead-foil strips are embedded in the rubber to provide fluoroscopic identifica-

From the Cardiopulmonary Laboratory, Firland Sanatorium and the Department of Medicine, University of Washington.
*Supported in part by research grants G3389 and H1892 from the National Institutes of Health, U. S. Public Health Service.
Presented before the Interim Session, American College of Chest Physicians, Seattle, Washington, November, 1956.

tion of the channels during intubation. Since the left main bronchus is considerably longer than the right, it is seldom feasible to use the same catheter for studies on both sides, and we have therefore built right- and left-handed models. In the right lung, anatomical considerations require that the middle lobe be measured with the lower lobe.

Intubation

With pre-medication and under topical anesthesia, intubation is carried out as for routine bronchospirometry. A spring-steel, wire guide is inserted into the lower lobe channel, and bent to the proper angle to quide the catheter into the trachea. The configuration of the upper lobe channel at the distal end of the catheter may make introduction of the tip through the glottis troublesome. This aspect of intubation may be simplified by bending the laterally projecting, upper-lobe channel parallel with the lower-lobe channel, and then exhausting the residual air in the distal balloon. The vacuum in this balloon holds the two channels parallel until they have entered the trachea. The wire guide is then removed.

Under fluoroscopic control, the catheter is then placed in the appropriate main stem bronchus. The vacuum in the distal balloon is released and the catheter is rotated and moved up and down until the upper lobe channel suddenly moves laterally and engages in the upper lobe bronchial orifice. The distal balloon is then inflated until traction on the catheter meets with resistance, and does not dislodge the channel from its position within the upper lobe bronchial orifice. Care must be taken not to inflate this balloon more than is necessary to stop leakage, since with

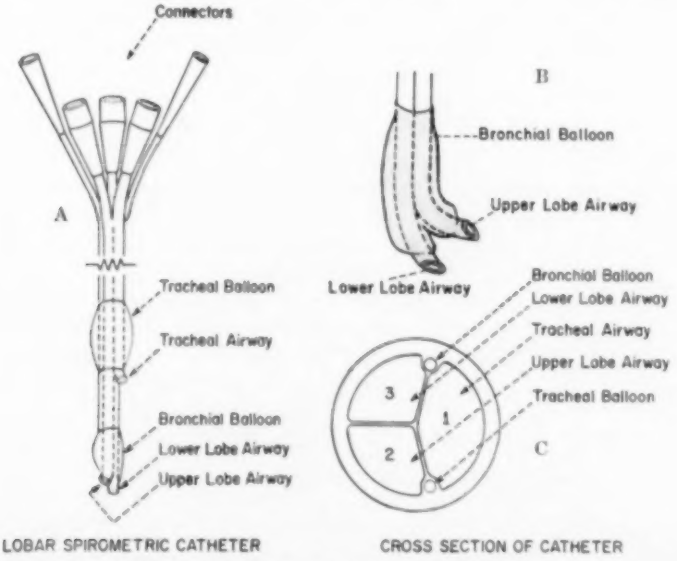


FIGURE 1: Lobarspirometry catheter, arrangement of the three airways and isolation balloons is shown in A, the detail of the tip in B, and the cross section in C.

over-inflation, the coryna may be pushed aside and compromise the bronchus to the contralateral lung.

When the catheter is firmly in place, the subject lies supine, and recording spirometers are attached to each of the three airways. The proximal balloon is inflated, and simultaneous recordings are made from the upper lobe, the lower lobe, and the contralateral lung. If the functional isolation of each unit is complete, no spirometer will record a loss of volume. Weighting of one spirometer bell will not cause either of the others to rise if the seal in the balloons is adequate. A vital capacity maneuver must not reveal any obstruction. As an additional check, we have routinely used the nitrogen meter to sample one unit while 100 per cent oxygen is ventilating the others. When the check for the adequacy of the functional isolation is complete, the usual recordings of oxygen uptake and ventilation may be made.

To determine the flow characteristics of the lobar spirometric and two commonly used bronchospirometric catheters (Zavod and Carlens), an E. Greiner flow meter was mounted in series with the catheters. The connector had a lateral arm leading to a water manometer. The catheters selected for testing had similar outside diameters (14mm.). The resistance to air flow through the combined upper- and lower-lobe lumina of the lobar catheter is almost identical to that in the left lumen of the Carlens bronchospirometric catheter (Fig. 2). The flow resistance in the Zavod catheter is markedly greater than those in the other two. Individually determined, the flow resistances of the upper- and lower-lobe lumina are almost equal.

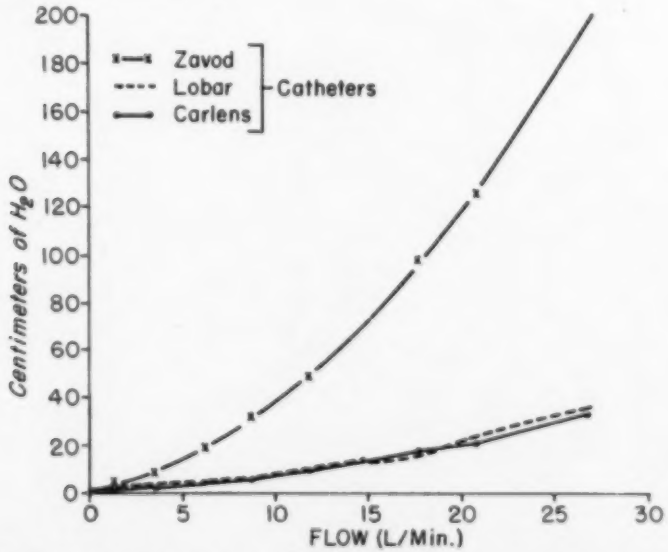


FIGURE 2: Flow characteristics of the lobarspirometric catheter and left side lumen of two standard catheters (Zavod and Carlens). Upper- and lower-lobe lumina combined on the lobarspirometric catheter.

Similar comparison of tracheal lumina of the three catheters results in a plot of flow resistance similar to that in Figure 2. The same general relationship among the three catheters in the same ranges of value is also found when flow and pressure in the short lumina are measured.

Possible Uses for Lobarspirometry

This lobarspirometric catheter was originally designed for specific research purposes, and the experience gathered during its use in 25 right-sided and 5 left-sided lobar studies confirms its usefulness in such areas as the investigation of pressure volume gradients, the mechanics of lung motion, and the study of perfusion differences accompanying changes in body position.

However, our experience also indicates that this catheter may be used to provide data available in no other way. Thus, in those patients whose pulmonary function is severely reduced, data obtained by use of this catheter may allow salvage by pulmonary resection. Also, this catheter can often be used when abnormalities of the tracheobronchial tree prohibit the use of the standard bronchospirometric procedures.

SUMMARY

We have described a new three-lumen catheter designed to allow oxygen uptake and ventilatory studies to be simultaneously performed on the upper and the lower lobe of one lung and on the entire contralateral lung. Some general areas where this catheter may be very useful have been indicated.

RESUMEN

Hemos descrito un catéter de tres luces ideado para permitir el ingreso de oxígeno y hacer estudios ventilatorios simultáneamente en los lóbulos inferior y superior de un pulmón y en el contralateral completo. Se señalan algunas indicaciones útiles para este catéter.

RESUME

Les auteurs ont décrit un nouveau cathéter à trois lumières établi pour permettre l'arrivée d'oxygène et des études ventilatoires portant simultanément sur le lobe supérieur et inférieur d'un poumon et sur la totalité de l'autre poumon. Les auteurs ont donné quelques indications générales pour lesquelles cette sonde pouvait être de grande utilité.

ZUSAMMENFASSUNG

Wir haben einen neuen Katheter mit drei lumina beschrieben, der die Aufgabe hat, die Sauerstoffaufnahme zu gestatten und ventilatorische Studien gleichzeitig vom oberen und unteren Lappen einer Lunge und der ganzen kontralateralen Lunge zu ermöglichen. Es wurden einige allgemeine Anwendungsgebiete aufgezeigt, bei denen dieser Katheter eine nützliche Verwendung finden kann.

REFERENCES

1 Breton, A. and Mereau, J.: "Interet des Epreunes Fonctionnelles Respiratiores par Airs Separes en Chirurgie Thoracique," *Le Poumon*, 3:335, 1947.

2 Carlens, E. and Mattson, S. B.: "Lobar Ventilation and Oxygen Uptake in Man: Influence of Body Position," *J. Thoracic Surg.*, 30:676, 1955.

3 Martin, C. J., Cline, F. and Marshall, H.: "Lobar Alveolar Gas Concentrations; Effects of Body Position," *J. Clin. Investigation*, 32:617, 1953.

The Use of Trypsin in the Therapy of Tuberculous Lymphadenitis and Tuberculous Fistulae*

CHAIM RAPOPORT, M.D.**
Beer Yacov, Israel

This report deals with nine cases of tuberculous lymphadenitis treated with trypsin in sesame oil and uninterrupted antituberculosis drugs. Follow-up periods varied from eight to 16 months, including histopathological evaluation of the results of treatment.

Antituberculous drugs in tuberculous lymphadenitis have been in general disappointing. The natural course of tuberculous lymphadenitis with its alternating periods of quiescence and relapse make it difficult to evaluate those few cases that have met with apparently successful treatment. The disappointment is more deeply felt as other forms of primary tuberculous and fresh exudative lesions have responded so well to the drug now in use. We felt that any additional factor that will enhance the phagocytic power of the mononuclear cells[1, 3, 4] and open up vascular channels to the site of the causative factor of the disease for the drugs in use may be helpful in overcoming the infection.[2, 6] With this in mind, pure crystalline trypsin in sesame oil,† each ml. containing 5 mg., was administered intramuscularly simultaneously with various antituberculous drugs.

Methods:

We selected only those cases where unequivocal evidence of tuberculous etiology was present and which under prolonged drug treatment did not improve or become progressively worse. In every case we had biopsy or culture for Koch's bacillus before the start of treatment, where feasible during treatment, and in all cases at the end of treatment. Each case had x-ray films of the neck, chest, spine and appropriate bones. Routine blood studies, urine examinations, liver function tests, and ECG were performed at the start, during, and on termination of treatment. The cases were examined daily on the ward. Trypsin was administered intramuscularly in combination with one or more of the following: Rimifon, para-aminosalicylic acid and streptomycin.

Case 1: P. Sh. Hospital No. 30074. This girl of eight years was referred to our hospital because of masses in the right axilla with multiple draining sinuses and a protruding fluctuating mass below the right clavicle. Tissues were indurated and edematous. She had been hospitalized from March 1953 until July 1954 because of tuberculous lymphadenitis collis and because of multiple cold abscesses located in various parts of the chest and right axilla. X-ray films of the chest in 1953 showed enlarged mediastinal lymph nodes as well as atelectasis of the anterior segment of the right upper lobe. She had received a total of 18 Gm. Rimifon and 2.2 kg. of PAS. Her general condition was improved following treatment, the sedimentation rate dropped from 80 mm. per hour to 10 mm. per hour upon discharge. The draining fistula closed. While in the

*This report is based on work done in Malben's Tuberculosis Hospital in Israel, which is supported by the American Joint Distribution Committee which receives its funds through the United Jewish Appeal.

**Head of Department, Malben's Tuberculosis Hospital.

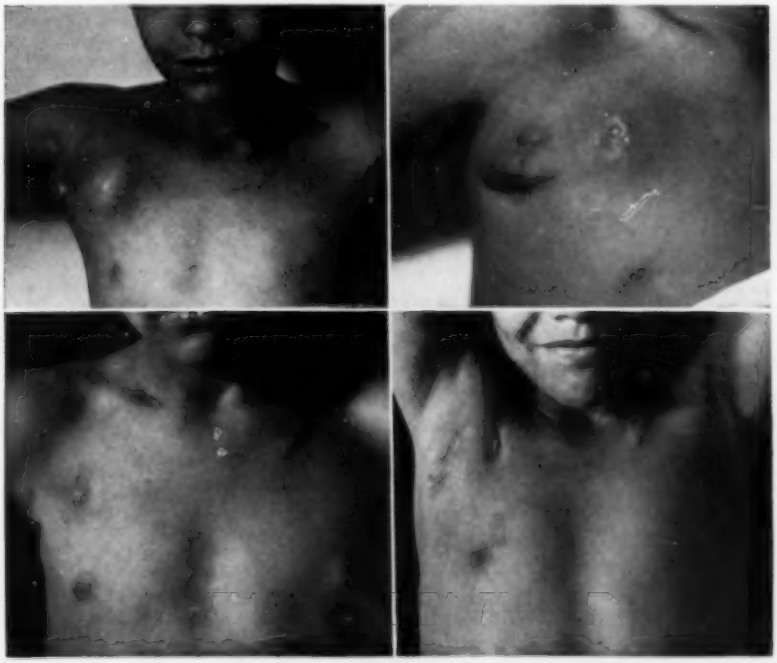
†Parenzyme: The National Drug Company, Philadelphia, Pennsylvania.

outpatient clinic, the enlarged nodes in the right axilla reappeared, the fistula re-opened and the discharge was positive for Koch's bacillus on culture.

Local PAS ointment was given without success and she was admitted to our hospital in May 1955. She was toxic, and her temperature was 39-40°C. Physical examination revealed a large mass in the right axilla, consisting of multiple matted nodes, and numerous draining fistulae. In addition, a large swelling (6x8 cm. in diameter) was present below the right clavicle. X-ray films of the chest, spine, neck, and ribs were negative. Puncture aspiration of the abscess below the clavicle revealed pus which contained Koch's bacilli. Swabs from the sinuses showed Staphylococcus aureus, coagulase positive, sensitive to Achromycin. Treatment with Achromycin was started, following which the temperature dropped to normal and her general condition improved. However the local appearance of the lesions remained unchanged. Drainage from the sinuses continued unabated. After eight cultures came back positive for Koch's bacillus, including two guinea pig inoculations, on June 29, 1955, simultaneous treatment with Rimifon and trypsin was started. Trypsin was given intramuscularly for 10 days (a total of 50 mg., 5 mg. daily in two divided doses). Rimifon was continued for an additional two weeks after stoppage of the trypsin; a total period of Rimifon administration was 24 days, totalling 3 gm. On the sixth day of treatment the old fistulae were almost closed and the new fistulae formed at the base of puncture of the fluctuating mass below the right clavicle started healing with healthy granulation tissue at its base. By the end of July 1955, which is one month after initiation of treatment, all fistulae were closed and replaced by firm scar. The mass in the right axilla decreased markedly, only rudimentary small nodes were palpable in that region; sedimentation rate dropped from the original 50 mm. to 16 mm. per hour. She remained clinically well and under observation in the hospital.

In December, 1955, in view of the contemplated biopsy of the residual nodes, Rimifon was re-started on a daily dosage of 150 mg. and continued until March 18, 1956, on which day the residual nodes were removed. The histological report follows: Fibrosis of lymph nodes without histological evidence of tuberculosis. Concentration and culture for Koch's bacillus as well as guinea pig inoculation removed at the biopsy from different areas were negative.

For the last seven months she has been clinically well.



Case 1

Case 2: A. B. Hospital No. 36285. This girl of 13 years had a swelling detected in the right side of the neck in January 1955. This gradually enlarged and she was referred to the Chest Clinic with the diagnosis of tuberculous lymphadenitis collis. X-ray film of the chest showed calcified nodes in the right hilum as well as a calcification in the apex of the lower lobe of the right lung. X-ray film of the neck showed multiple calcifications bilaterally. On physical examination a fluctuating mass beneath closely knitted nodes was palpable. Aspiration in March 1955 revealed pus that was sterile on general culture and negative for Koch's bacillus. Following aspiration a draining fistula appeared. This was treated for two months with Rimifon and PAS, a daily dosage of 150 mg. and 5 gm. respectively. A total of 7 gm. Rimifon and 500 gm. PAS was given until transfer to our ward. On admission in June 1955 a continuously draining fistula was present. Underlying it was a big palpable node. The area surrounding the fistula was red and edematous. After two weeks of observation without treatment and without change in the local condition, trypsin, 5 mg. daily, and Rimifon, 150 mg. daily, were administered. On the fourth day of treatment the fistula was closed and crusted. Trypsin was given for seven days and Rimifon 14 days. A firm scar was seen after three weeks of drug. She remained in the hospital for nine months without additional treatment. The scar remained firm, the underlying node became small but palpable. After nine months of observation the nodes were removed.

Histo-pathological studies revealed eosinophilic staining clumps which appeared to be disintegrating acid-fast bacilli. Tuberculous lymphadenitis active.

Culture for Koch's bacillus and guinea pig inoculation of the biopsy material were negative.

The wound healed, and she was discharged clinically well after three months' additional hospital observation and remained so until December, 1956.

Case 3: A. T. Hospital No. 33419. This girl of five years was hospitalized in another institution from August 30, 1954 to January 16, 1955. She was admitted to the a/m institution because of extensive tuberculous cervical and mediastinal lymphadenitis with secondary atelectasis in the right lower and middle lobes. Her general condition was poor. On extensive combined antituberculous drugs including local administration there was little improvement. She had 28 gm. of streptomycin, 5 gm. Rimifon, and 250 gm. PAS. Biopsy of cervical nodes and those of the groin showed active tuberculous lymphadenitis. Following biopsy the wound remained open and drained for a long time. She was admitted to our ward in January 1955 with the findings above described. It was decided to keep her under observation without drugs for eight months. During this period she led a normal life and attended kindergarten and the clinical condition markedly improved. She gained weight, developed mentally, the nodes in the neck and mediastinum decreased in size and were hardly palpable in the exposed region. In September 1955 antituberculosis drugs were started because of appearance of productive cough. Rimifon, 100 mg., and streptomycin, 1/4 gm. every third day, were given. In March 1956, while she was still receiving drugs, lymph nodes enlarged in the submaxillary and left axillary regions. A submaxillary node region removed on April 9, 1956 showed evidence of tuberculous lymphadenitis with extensive caseation and recent liquefaction. Smudges of eosinophilic staining were present, which appeared to be disintegrating tubercle bacilli. On April 9, trypsin was added in a dosage of 5 mg. daily to the previously administered antibiotics and continued until May 6, 1956. A total of 75 mg. of trypsin was administered. On May 6, 1956, the node in the left axilla which decreased in size during the period of treatment was removed for biopsy. This revealed chronic lymphadenitis, evidence of tuberculosis. Cultures and guinea pig inoculation were negative for Koch's bacilli. Trypsin and antituberculosis drugs were continued and the large node in the submaxillary region, adjacent to the one biopsied on May 9, 1956, was markedly decreased in size. On May 20, 1956, or three weeks after initiation of the treatment, node was removed. (A total of 100 mg. of trypsin had been given.)

It contained granulomatous lesion with considerable fibrosis, apparently tuberculous. Culture and guinea pig inoculation were negative.

She has remained clinically well without treatment for the last eight months.

Case 4: O. S. Hospital No. 30087. This girl of 10 years was hospitalized for the first time in December 1951 because of cervical and mediastinal tuberculous lymphadenitis. From December 1951 until January 1955 she received interrupted combined antituberculosis drugs (total of 1.5 Kg. PAS, 20 gm. streptomycin, and 15 gm. of Rimifon) in addition to x-ray therapy, heliotherapy and local PAS application to draining fistula. On admission to our hospital in January 1955 multiple cervical nodes varying from 5 to 25 mm. in diameter were present in addition to scars of previous sinuses. No special treatment was administered until May 1956. During this one and one-half years of observation, the cyclic nature of the appearance of the cervical nodes was confirmed. Every four and one-half to six months the nodes had previously enlarged, reached a maximum size, and subsided within four to six weeks. On May 7, 1956,

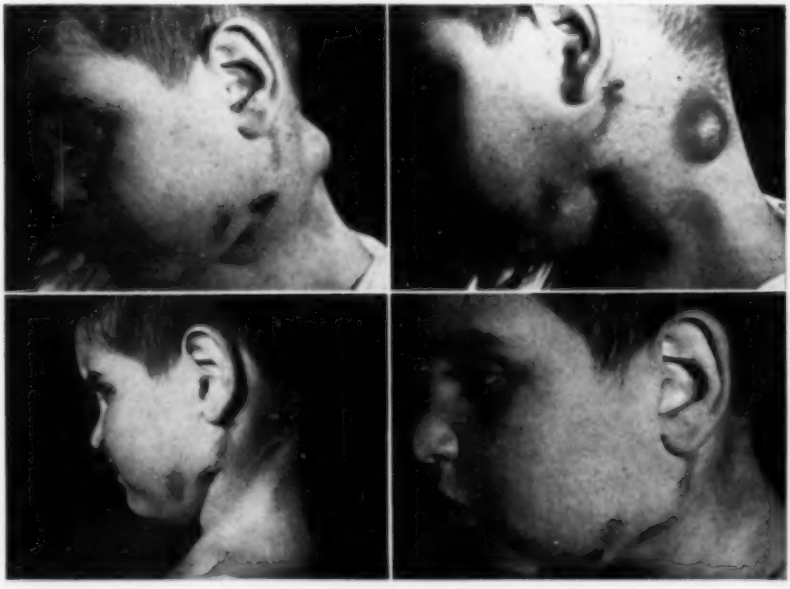
biopsy of a node revealed a granulomatous lesion, probably tuberculous. Complete bacteriological studies were negative for Koch's bacillus.

On May 9, 1956, she was started on trypsin, 5 mg. daily in two divided doses; Rimifon, 100 mg. daily; and streptomycin, 1/4 gm. every third day. During the next four months the antituberculosis drugs were given but trypsin was discontinued after 46 days. Marked clinical improvement took place and most of the nodes disappeared. Biopsy on September 3, 1956 revealed fibrosis in addition to changes of chronic inflammation, non-specific in the small nodes and areas of caseation, partially surrounded by fibrous capsules with evidence of specific granulation tissue with epithelioid cells and giant cells of Langhans' type in the large nodes.

Case 5: F. R. Hospital No. 396669. This girl of 10 years was admitted to our ward on June 4, 1956. Previous to admission she had received 100 mg. of Rimifon daily since April 1956. On admission a large profusely draining crater was overlying the second portion of the sternum. The process was in the first and second portion of the sternum with marked periostial reaction. X-ray film revealed enlarged mediastinal lymph nodes and soft infiltrations bilaterally. Pus from the draining ulcer contained Staphylococcus aureus coagulase positive and C. diphtheriae sensitive to all antibiotics.

On July 6, 1956, the lesion appeared unchanged and trypsin (5 mg. daily in two divided doses) together with Rimifon (150 mg. daily) and PAS (6 gm. daily) were started. On August 8, 1956, a firm scar was present in the place of the previous deep crater and x-ray film of the sternum, dated August 1, 1956 (three weeks after start of treatment), showed marked sclerosis of the bone lesion and striking decrease in periostial reaction. A total of 85 mg. of trypsin was given.

Case 6: M. B. Hospital No. 34181. This boy of five years was referred to our hospital because of tuberculous lymphadenitis collis with draining fistulae. He had been under treatment since 1951 and had received, until May 1954, 60 gm. of streptomycin, 1 Kg. of PAS, as well as 12 x-ray radiations with only temporary relief. From May 1954 he had received Rimifon and PAS without improvement. When admitted here on November 1, 1955 he had large left cervical masses with multiple draining sinuses and at the angle of the jaw on the same side. X-ray film of the neck showed large calcified nodes bilaterally with surrounding area of tumefaction. His temperature was 39-40°C. and he was highly toxic. Trypsin, 5 mg. daily, in two divided doses, together with Rimifon, 150 mg. daily were started November 28, as there was no improvement since admission. Three weeks after this treatment was started the sinuses were closed and the masses were strikingly diminished. On March 1, 1956, trypsin



Case 6

was stopped and Rimifon continued until March 2, 1956. At the time the trypsin was stopped, firm scars existed in the place of the previous sinuses. A total of 150 mg. of trypsin had been given up to this time. On April 3, 1956, trypsin was re-started in the previous dosage preparatory to the intended biopsy of the underlying nodes. Biopsy on May 20, 1956, revealed two groups of nodes. The large calcified node showed a minimal activity tuberculosis process while the lymph nodes underlying the scar contained only lymphoid hyperplasia. Multiple smears, cultures, and guinea pig inoculations of the biopsied material (both groups) were negative for Koch's bacillus.

On July 3, 1956, trypsin was added to the antituberculosis drug in use and continued until September 3, 1956. Then two nodes were removed from the right side of the neck, which were reported as calcified on admission. The small gland showed evidence of chronic non-specific inflammation, with proliferation of the reticuloendothelial system. The large node showed evidence of chronic non-specific inflammation, at the periphery, as well as proliferation and enlargement of the lymph follicles. In the center a wide area of caseation surrounded by wide mantle of fibrosis was seen. No specific granulation tissue was identified.

Case 7: S. H. Hospital No. 37372. This man of 33 years was admitted to our hospital on October 7, 1955. In May 1954 a large mass appeared under the right clavicle. This fluctuating mass burst open and drained continuously. In May 1955, after Koch's bacillus was found antituberculosis drugs were started and 36 gm. of Rimifon, 700 gm. of PAS, and 4 gm. of streptomycin had been administered. An x-ray film of the chest at that time showed involvement of the first rib on the right side. In our hospital on November 1, 1955, tuberculous granulation tissue was removed behind the first rib, partial resection of the first rib was performed, and wide excision of the tracts was done.

Culture for Koch's bacillus of this granulation tissue was positive for Koch's bacillus. Following operation wound healed. He received a total of 62 gm. of streptomycin and 18 gm. of Rimifon. In January 1956 the wound was closed when he was discharged. On March 15, 1956, he was readmitted because of multiple draining fistulae at the site of the operation. The remaining segment of the first rib removed, and the fistula tract excised on March 18, 1956 and tuberculous granulation tissue was found.

The fistulae remained open and discharging pus, although PAS, streptomycin, and Rimifon daily were continued to a total of 87 gm. of streptomycin, 108 gm. of Rimifon, and 250 mg. PAS, not counting the amounts of antibiotics given to him from May until October 1955 in the outside institutions.

On the first of August, 1956, trypsin was added in a dosage of 5 mg. daily in two divided doses to the combined antituberculosis drugs. After three weeks the fistulae were filled in with healthy granulation tissue and by the end of six weeks firm scars were present.

Case 8: M. H. Hospital No. 39632. This boy of 12 years was referred to us from another institution on June 3, 1956. He received 51 gm. of streptomycin and 600 gm. of PAS from March 30, 1956, until May 30, 1956. On admission he had enlarged nodes in both axillae with multiple scars. X-ray film of the spine showed destruction of vertebrae from D3 to D6 as well as a cold abscess. Antituberculosis drugs were continued including 4 gm. of Rimifon, 2 gm. of streptomycin, and 140 mg. of PAS. On June 23, 1956, a lymph node was removed from a large packet of glands in the right axilla. This contained a cavity lined by a broad zone of tuberculous granulation tissue surrounded by lymphocytic infiltration and wide mantle of fibrosis. No acid-fast bacillus was seen.

Culture and guinea pig inoculation were negative. Following biopsy trypsin was given for two months in a dosage of 5 mg. daily together with the antituberculosis drug.

On September 4, 1956, no lymph node could be visualized on dissection.

No acid-fast bacilli on smear. A lump removed proved to be subcutaneous tissue attached to skin. A few foci composed of epitheloid cells and giant cells of Langhans' type were present but there was no caseation. Acid-fast bacilli were not found. The wound healed per primam.

Case 9: T. A. Hospital No. 33083. This girl of five years was admitted on January 23, 1955, without available history. A large group of nodes was visible overlying the right parotid area. They were swollen and tender. The skin edematous and inflamed. Trypsin *without* antituberculosis drugs was given for one week with marked subsidence of the inflammatory reaction. Between September 15, 1955, and April 19, 1956 she received 15 gm. of streptomycin and 17 gm. of Rimifon. On April 19, 1956, a removed node revealed extensive caseation with focal calcification, the surrounding reaction of tuberculous granulation tissue was narrow, and there was slight fibrosis. Drugs were continued as before, and trypsin was added from June 1956 until September 4, 1956, in usual dosage.

On September 4, 1956, a lymph node showed marked proliferation of the lymph follicles. In the center of the node specific granulation tissue partially caseated was

seen surrounded by collagen. Acid-fast bacilli were not found on smear. At the time of the last biopsy doubt existed in the surgeon's mind whether any node was left for excision.

SUMMARY AND CONCLUSIONS

1. Seven cases of tuberculous lymphadenitis and two cases of bone tuberculosis (sternum and first rib) with tuberculous fistulae were treated.

2. All had previous antibiotic treatment without success for periods varying from four months to four years.

3. Treatment with trypsin given simultaneously with antibiotics effected a clinical cure within a period varying from three to six weeks.

4. Clinical healing was evidenced by a marked decrease in size of nodes, disappearance of nodes, closure of fistulae and scar formation. This does not imply cure from the histo-pathological point of view.

5. Bone tuberculosis healed more rapidly.

6. From a histo-pathological point of view all the biopsies performed at intervals and at the end of treatment showed either marked improvement of the histological picture or evidence of complete healing. The rich deposition of collagen in healed lesions is noteworthy. The material of the biopsied nodes at the end of treatment was negative on smear, culture and guinea pig inoculation for Koch's bacillus.

7. The schedule of treatment advised is as follows: Trypsin 5 mg. daily in two divided doses for six weeks, simultaneously with uninterrupted antibiotics, Rimifon and PAS daily for six months. An additional course of trypsin of three weeks' duration at the termination of the six months' period. No side effect was noted during treatment.

8. *Trypsin administered together with antibiotics appears to be the treatment of choice of tuberculous lymphadenitis and tuberculous sinuses, secondary to the above, or bone tuberculosis.*

CONCLUSIONES

1. Se trataron siete casos de linfadenitis tuberculosa y dos de tuberculosis ósea (esternón y primera costilla), con fístula.

2. Todos habían tenido tratamiento con antibióticos de cuatro meses a un año antes.

3. El tratamiento con tripsina dado simultáneamente con los antibióticos logró una cura clínica dentro de un tórmino variando de tres a seis semanas.

4. La curación clínica se evidenció por un marcado decrecimiento del tamaño de los ganglios, desaparición de ellos, cierre de fístulas y formación de cicatrices. Esto no implica curación desde el punto de vista histopatológico.

5. La tuberculosis ósea curó más rápidamente.

6. Desde el punto de vista histopathológico, todas las biopsias realizadas a intervalos y al final del tratamiento mostraron ya sea mejoría o evidencia de curación. Es de notarse la elevada acumulación de colágena en las lesiones curadas.

El material de los ganglios a la biopsia al fin del tratamiento fué negativo al frotis, cultivo e inoculación al cuy, para el bacilo de Koch.

7. El tratamiento es com sigue: Se dan 5 mg. de tripsina diarios en dos

dosis por seis semanas simultáneamente con antibióticos sin interrupción, Rimifón y PAS diariamente por seis meses. Una serie adicional de tripsina por tres semanas se da al terminar el período de seis meses. No se notaron efectos colaterales.

8. La tripsina administrada junto con los antibióticos parece ser el tratamiento de elección de la linfadenitis tuberculosa, así como de las fístulas tuberculosas secundarias a la anterior o de la tuberculosis ósea.

RESUME

1. L'auteur a traité sept cas d'adénopathies tuberculeuses et deux cas de tuberculose osseuse (sternum et première côte) avec fistules.

2. Tous avaient reçunum traitement antibiotique sans succès pendant une période de 4 mois à 4 ans.

3. Le traitement par la trypsine associée aux antibiotiques amena la guérison clinique dans un laps de temps de 3 à 6 semaines.

4. La guérison clinique fut objectivée par la décroissance nette de la taille des ganglions, leur disparition, la fermeture des fistules et la constitution d'une cicatrice. Ceci ne veut pas dire qu'il y ait guérison complète au point de vue histologique et anatomo-pathologique.

5. La tuberculose osseuse évolua plus rapidement vers la guérison.

6. Du point de vue histologique et anatomo-pathologique, toutes les biopsies pratiquées à intervalles réguliers et à la fin du traitement montrèrent soit une amélioration nette des aspects histologiques soit une guérison complète. La présence d'un dépôt abondant de collagène dans les lésions guéries mérite d'être noté. Les produits de biopsie ganglionnaire en fin de traitement ne contenaient plus de bacilles de Koch décelables soit par frottis, soit par culture, soit par inoculation au cobaye.

7. Le programme du traitement qui a été suivi est le suivant: trypsine: 5 mmg. par jour en deux doses pendant six semaines, associée aux antibiotiques Rimifon et P.A.S. administrés de façon ininterrompue chaque jour pendant six mois. Une série supplémentaire de trypsine d'une durée de trois semaines à la fin de six mois. On ne nota aucun effet secondaire pendant le traitement.

8. La trypsine administrée avec les antibiotiques semble être le traitement de choix des adénopathies tuberculeuses et des fistules qui peuvent leur faire suite ainsi que de la tuberculose osseuse.

SCHLUSSFOLGERUNG

1. 7 Fälle von tuberkulöser Lymphadenitis und 2 Fälle von Knochentuberkulose (Brustbein und erste Rippe) mit tuberkulösen Fisteln wurden behandelt.

2. Alle hatten zuvor eine antibiotische Behandlung gehabt, die ohne Erfolg geblieben war und zwar in Zeitsbschnitten zwischen 4 Monaten und 4 Jahren.

3. Behandlung mit Trypsin in Verbindung mit Antibioticis bewirkte eine klinische Heilung in einen Zeitraum von 3-6 Wochen.

4. Klinische Heilung wurde augenscheinlich gemacht durch eine ausgesprochene Abnahme in der Grösse der Knoten, einem Verschwinden der Knoten, Fistelverschluss und Narbebildung. Dies besagt nicht Heilung vom pathologisch-histologischen gesichtspunkt.

5. Knochen tuberkulose heilte schneller.

6. Vom pathologisch-histologischen Standpunkt gesehen, zeigten alle in Intervallen und am Ende der Behandlung durchgeführten Biopsien entweder eine ausgesprochene Besserung des histologischen Bildes oder den Augenschein einer kompletten Heilung. Die reichliche Ablagerung von Bindegewebe in geheilten Herden ist bemerkenswert. Das Material der Biopsien der Lymphknoten am Ende der Behandlung war auf Koch'sche Bazillen negativ im Ausstrich, in Kutur und Tierversuch.

7. Das empfohlene Behandlungschema besteht in Trypsin 5 mmg tägl. in zwei geteilten Dosen auf 6 Wochen gleichzeitig mit pausenlosen Antibioticis, Rimifon und PAS täglich auf 6 Monate, eine zusätzliche Folge von Trypsin von drei Wochen am Ende der ½-Jahres-Periode. Es wurden keine Nebenwirkungen während der Behandlung beobachtet.

8. Trypsin bei Verwendung in Verbindung mit Antibiotics scheint die Behandlung der Wahl zu sein bei der tuberkulösen Lymphadenitis und bei tuberkulösen Fisteln als Folge derselben, oder bei Knochentuberkulose.

REFERENCES

1 Innerfield, L., Angrist, A. and Schwarz, A.: "Parenteral Administration of Trypsin: Clinical Effect in 538 Patients," *J.A.M.A.*, 152:597, 1953.

2 Ponder, E.: "Effects Produced by Trypsin in Certain Properties of Human Red Cell," *Blood*, 6:350, 1951.

3 Innerfield, I., Angrist, A. and Benjamin, J. W.: "Studies on Trypsin; Anticoagulant Action of Trypsin," *Gastroenterol.*, 20:630, 1952.

4 Innerfield, I., Schwarz, A. and Angrist, A.: "Intravenous Trypsin: Its Anticoagulant, Fibrinolytic and Thrombolytic Effects," *J. Clin. Invest.*, 31:1049, 1952.

5 Innerfield, I.: "Trypsin Given Intramuscularly in Chronic Recurrent Thrombophlebitis," *J.A.M.A.*, 156:1056, 1954.

6 Tabachnick, J. and Weiss, C.: "Mechanism of Softening of Tubercles. IV. Digestion of Caseous Tubercles by a Proteinase Extracted from Polymorphonuclear Leucocytes," *A.M.A. Arch. Path.*, 61:76, 1956.

The Endoscopic Treatment of Parenchymal Tuberculosis

(A Pilot Study in the Human)

A. ALBERT CARABELLI, M.D., F.C.C.P.

Trenton, New Jersey

To date the therapy of pulmonary tuberculosis has been more or less confined to three main categories: compression, extirpation, and chemotherapy. There have been many variations of each procedure and frequently any of the three have been used in combination. The selection of the particular type of therapy or combination has been more or less standardized and to date one sees pneumothorax on the wane; extirpation on the rise; and chemotherapy predominant.

With respect to chemotherapy, review of the literature shows that the trend is towards the almost universal use of isonicotinic acid hydrazide (INH) in combination with streptomycin (SM) or para-aminosalicylic acid (PAS). Dosage of these drugs has been commonly accepted at 4 mg/K, 1-2 grams/week, and 12 grams/day, respectively.

It is interesting to review the literature to date on the chemotherapeutic results in parenchymal tuberculosis, pointing out the salient features and the gross averages in results: All the authors reviewed[1, 2, 3, 4, 5] have used INH alone or in combination with SM or PAS in the dosage indicated above. The period of treatment varied from one to 32 months. Sputum conversion was from 5-100 per cent with any increase more or less proportionate to the length of time treated. In all cases the determination of negativity depended on *expectorated* spittles or on *gastric studies*. With respect to the constitutional symptoms all authors are in accord with the usual increase in weight, subsidence of toxic manifestations, and the general beneficient effect of INH on the body and psyche. With respect to the x-ray film changes there is reported an over-all improvement in about 60 per cent of cases. Cavity closure was noted in about 30 per cent and diminution in size in 21.5 per cent. Clearing of the exudates was recorded at 24 per cent. There is general agreement that fibrous lesions, calcified areas, thick-walled cavities and old fibro-caseous focii remained unchanged; and that, in many instances, little change is noted in the x-ray film status of the lesion in spite of the conversion, weight gain and sense of well-being. Most of the improvement, often with dramatic clearing, is noted in the recent lesion of an exudative nature. Another axiom in the roentgen observations is that if any im-

*Presented at the IV International Congress on Diseases of the Chest, Cologne, Germany, August, 1956.

**Chief of Thoracic Medicine, St. Francis Hospital, and Consultant in Thoracic Medicine and Bronchoesophagology, Trenton General Hospital, Trenton, N. J. Formerly Associate in Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

provement occurs, this takes place in the first three months and then such changes become progressively fewer and of lesser degree.

The following study concerns the exploration of an entirely new approach in the chemotherapy of parenchymal tuberculosis: namely, the *endobronchial* route. This concept is relatively new and few references are to be found in the literature.[6, 7] Before going into the details of its clinical aspects, however, it is important to outline certain basic anatomico-physiological as well as pathological phases of the fate of particulate matter within the lung. Special reference is made to the tubercle bacillus as well as the antituberculosis characteristics of several drugs for a better understanding of the rationale of this type of therapy.

Studies of the fate of particulate substances including the tubercle bacillus[9] introduced into the respiratory channels show a definite reaction on the part of the host to such invasion. The portion of this matter not immediately removed by cough penetrates the air passages and is carried to their finest subdivisions where it is subjected to reactions brought about by the protective forces indiginous to normal tissues. Phagocytosis is the first to function but is limited to particles less than 10 microns in size. The larger particles are not engulfed; they are promptly removed through the airways by the usual excretory function of entrapment in mucous secretions, ciliary motion, molding by the spiral bronchial musculature, and the expellent force of cough. Three cells—the polymorphonuclear leukocyte, the mononuclear alveolar cell, and the mononuclear cell which is believed to come from the blood—are the phagocytes concerned in removing particulate matter from the parenchyma; and this is done by way of the lymphatics. One mechanism is by way of the *superficial lymphatics*, which follow the first radicle of the pulmonary vein from the center of the primary lobule to its periphery and then course outward to join the subpleural plexus which in turn unite to form the lymph vessels that empty into the hilar nodes. The second is by way of the *deep lymphatics*, which follow the bronchial and vascular channels towards the hilar lymphnodes. Still a third method of excretion through the alveolar ducts, bronchioles, and bronchi exists but does not concern us in this study since it is non-contributory to the concentration of the drug in the parenchyma or lymphatics.

Once started, the lymphatic removal of particulate matter is rather rapid as can be seen following the introduction of graphite in the trachea when this substance will appear in the paratracheal nodes in about an hour. Tubercle bacilli similarly introduced have been culturally recovered from various organs 12 hours after introduction.

The superficial lymphatic route may be demonstrated by the presence of cells crowded together into irregular, ill-defined groups spaced at irregular, intervals along the course of the radicles of the pulmonary vein and in the subpleural lymphatic tissues. In these situations permanent lesions develop as anatomic tubercles when the foreign substance is the tubercle bacillus. The route of the deep lymphatics may be similarly traced by the temporary and permanent grouping of the phagocytic cells

along their course and also by observing the bronchial lymph follicles through and around which the lymphatics course. Often these vessels are crowded with degenerated phagocytic cells being carried out of the lung.

These observations would indicate that the introduction of particulate matter of antituberculosis activity directly into the bronchi would follow the same route taken by the tubercle bacillus and thus introduce bacteriostatic or bacteriocidal agents directly into focii usually involved by tuberculous infections. With such a portal of entry several advantages are obvious: firstly, a very high focal concentration of the drug may be possible which would remain in the lobe for an indefinite period (oily suspension); secondly, phagocytes loaded with engulfed drug particles are made the bearers of the noxious agent to the tuberculous focii proper and, with their death, release a therapeutic bomb; thirdly, bacilli-laden phagocytes will transport only non-viable bacilli to new focii since INH,

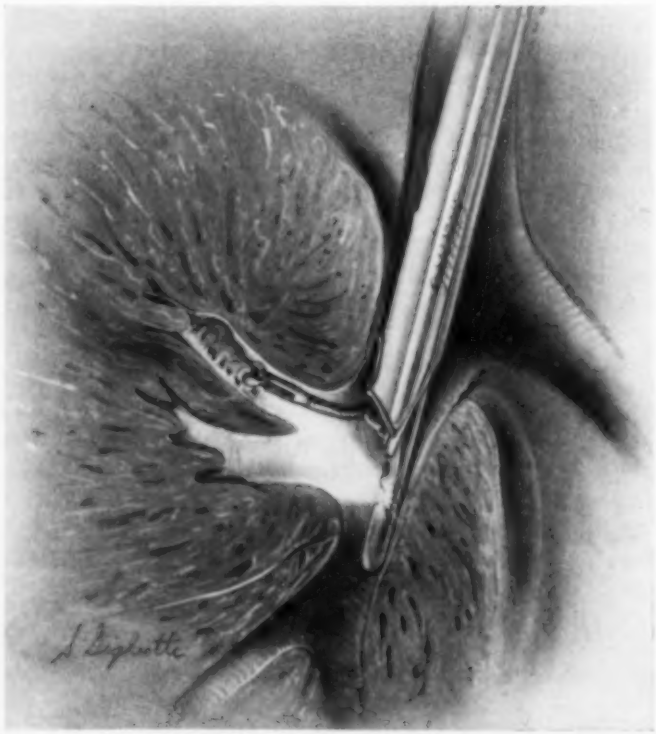


FIGURE 1: Upper lobe instillation with the Pentascope. This figure shows the instrument being used for biopsy. In instillation techniques a flexible woven catheter is substituted in lieu of forceps. Note possibility of segmental bronchus visualization and catheterization. In this case the apical segmental bronchus of the right upper lobe has been entered.

unlike SM, readily penetrates cell membranes in effective bacteriostatic or bacteriocidal concentration.[10, 11]

From the experimental animal and human studies[10, 11] it may be concluded that the oral administration of INH results in its concentration in the body fluids and plasma in direct proportion to any given dose whether in single or chronic administration; and that its retention is noncumulative since it is rapidly excreted from the urine, faeces, and saliva. The same studies indicate that the safe dose for chronic administration in man is an oral dose of 3-4 mg./K per day, which will result in a plasma concentration of 1.3-3.4 gamma/ml. The incidence of toxic reactions above these levels seems to be in direct proportion to the increased dosage.

It is obvious, that with the conventional oral dose, we are distinctly limited as to the amount of the drug which can be used safely. If we attempt to increase the dose on the supposition that a higher plasma concentration will have a stronger anti-tuberculosis effect, we are faced with a therapeutic frustration. Now, if the lung proper could be used as a therapeutic portal, we might be able to increase the concentration of the drug at the site of the disease without saturating the body as a whole and thus avoid any systemic toxic reactions. Such a concept might be feasible if a slowly absorbed preparation could be used which would saturate the lobe or lobes and still be ineffective in raising plasma levels to toxic thresholds. Herein lies the *concept of lobar or multi-lobar rather than body saturation.*

In the lung we have an anatomic *cul-de-sac* not equipped by nature for the rapid absorption or the chemical alteration of foreign substances as is the case with the intestinal tract. Physiologically the lung is highly specialized for gaseous exchange only; and for these purposes has a tremendous surface area. It also has a great potential for phagocytosis because of its richness in capillaries and lymphatics. It has been possible to instil substances of low absorption characteristics such as penicillin in oil into these passages with considerable clinical success (12); and it has long been known that such substances as lipiodol remain in residence for many months without any harm to the parenchyma proper or detectable impairment to the lobar physiology.

From the technical point of view it is presently possible to instrumentally reach many of the segmental and certainly all of the lobar bronchial levels for practical instillation of such substances.

It is interesting, on a purely gross theoretical basis, to calculate the drug concentration in one milliliter of lobar fluid when 10 cc. of an oily suspension containing 500 mg. of INH is introduced into a lobar bronchus. Using 991 grams as the average weight of the human lungs (33) and then considering the presence of six lobes by assuming the lingular division as a separate lobe, we arrive at an average lobar weight of 165 grams. Assuming that 90 per cent of this tissue is liquid matter, we could have a total of 148.5 mls. which eventually pick up 500 mgm. of INH. This would be equivalent to 3367 gamma/ml. of the drug. Again, on the assumption that 75 per cent is lost through the alveolar ducts, bronchioles, and bronchi, as well as dissipated to other organs and tissue fluids by

along their course and also by observing the bronchial lymph follicles through and around which the lymphatics course. Often these vessels are crowded with degenerated phagocytic cells being carried out of the lung.

These observations would indicate that the introduction of particulate matter of antituberculosis activity directly into the bronchi would follow the same route taken by the tubercle bacillus and thus introduce bacteriostatic or bacteriocidal agents directly into focii usually involved by tuberculous infections. With such a portal of entry several advantages are obvious: firstly, a very high focal concentration of the drug may be possible which would remain in the lobe for an indefinite period (oily suspension); secondly, phagocytes loaded with engulfed drug particles are made the bearers of the noxious agent to the tuberculous focii proper and, with their death, release a therapeutic bomb; thirdly, bacilli-laden phagocytes will transport only non-viable bacilli to new focii since INH,

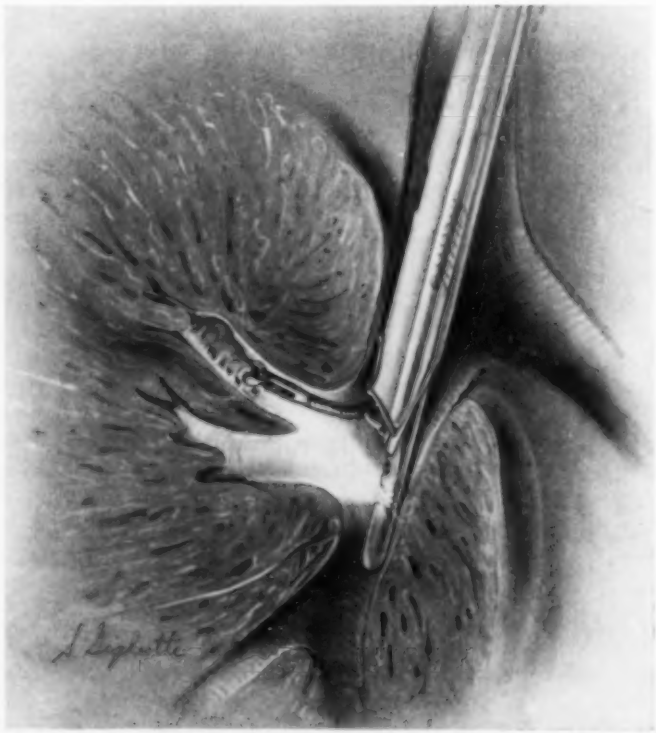


FIGURE 1: Upper lobe instillation with the Pentascope. This figure shows the instrument being used for biopsy. In instillation techniques a flexible woven catheter is substituted in lieu of forceps. Note possibility of segmental bronchus visualization and catheterization. In this case the apical segmental bronchus of the right upper lobe has been entered.

unlike SM, readily penetrates cell membranes in effective bacteriostatic or bacteriocidal concentration.[10, 11]

From the experimental animal and human studies[10, 11] it may be concluded that the oral administration of INH results in its concentration in the body fluids and plasma in direct proportion to any given dose whether in single or chronic administration; and that its retention is noncumulative since it is rapidly excreted from the urine, faeces, and saliva. The same studies indicate that the safe dose for chronic administration in man is an oral dose of 3-4 mg./K per day, which will result in a plasma concentration of 1.3-3.4 gamma/ml. The incidence of toxic reactions above these levels seems to be in direct proportion to the increased dosage.

It is obvious, that with the conventional oral dose, we are distinctly limited as to the amount of the drug which can be used safely. If we attempt to increase the dose on the supposition that a higher plasma concentration will have a stronger anti-tuberculosis effect, we are faced with a therapeutic frustration. Now, if the lung proper could be used as a therapeutic portal, we might be able to increase the concentration of the drug at the site of the disease without saturating the body as a whole and thus avoid any systemic toxic reactions. Such a concept might be feasible if a slowly absorbed preparation could be used which would saturate the lobe or lobes and still be ineffective in raising plasma levels to toxic thresholds. Herein lies the *concept of lobar or multi-lobar rather than body saturation.*

In the lung we have an anatomic *cul-de-sac* not equipped by nature for the rapid absorption or the chemical alteration of foreign substances as is the case with the intestinal tract. Physiologically the lung is highly specialized for gaseous exchange only; and for these purposes has a tremendous surface area. It also has a great potential for phagocytosis because of its richness in capillaries and lymphatics. It has been possible to instil substances of low absorption characteristics such as penicillin in oil into these passages with considerable clinical success (12); and it has long been known that such substances as lipiodol remain in residence for many months without any harm to the parenchyma proper or detectable impairment to the lobar physiology.

From the technical point of view it is presently possible to instrumentally reach many of the segmental and certainly all of the lobar bronchial levels for practical instillation of such substances.

It is interesting, on a purely gross theoretical basis, to calculate the drug concentration in one milliliter of lobar fluid when 10 cc. of an oily suspension containing 500 mg. of INH is introduced into a lobar bronchus. Using 991 grams as the average weight of the human lungs (33) and then considering the presence of six lobes by assuming the lingular division as a separate lobe, we arrive at an average lobar weight of 165 grams. Assuming that 90 per cent of this tissue is liquid matter, we could have a total of 148.5 mls. which eventually pick up 500 mgm. of INH. This would be equivalent to 3367 gamma/ml. of the drug. Again, on the assumption that 75 per cent is lost through the alveolar ducts, bronchioles, and bronchi, as well as dissipated to other organs and tissue fluids by

the blood stream, there might be, at any one time, a potential level of saturation of 842 gamma/ml. in the lobe concerned, uniformly disseminated according to the laws of osmosis, mass action, and phagocytosis. When this concentration is compared with the normal ranges of 1.3-3.4 gamma/ml. (plasma) obtained by standard oral medication, we can readily see the advantage of such a therapeutic portal if the clinical findings, host, and parenchymal tolerance, could justify such a procedure.

Another interesting observation in this respect is that animal studies[11] indicate that INH is broken down into isonicotinic acid and ammonia by enzymatic action in most organs, but that is not true in the lung (rat). If a parallel situation holds in the human, we have this added advantage to the use if the lung as a therapeutic portal.

Selection of the Drug of Choice

The fact that the preponderance of the literature in the chemotherapy of pulmonary tuberculosis centers about INH indicates that this particular

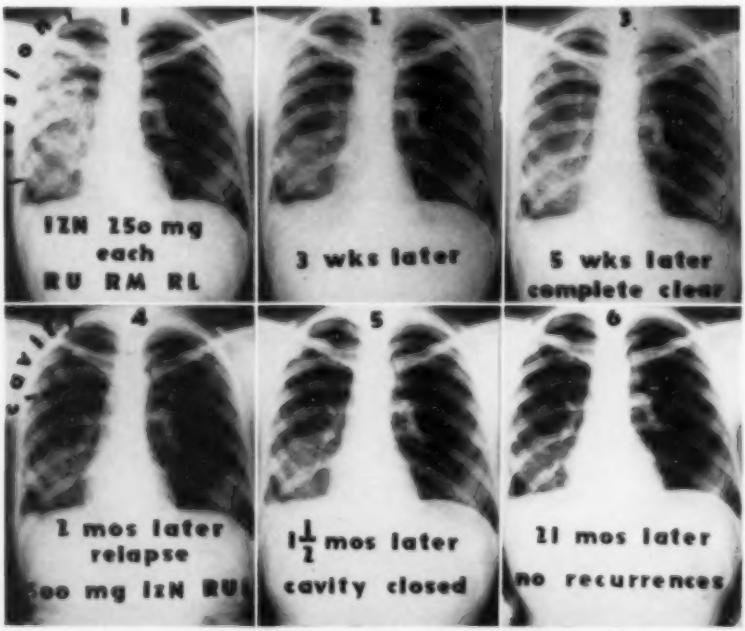


FIGURE 2: H. G., a white female, age 21, with a history of right-sided pulmonary tuberculosis treated successfully with pneumothorax from 1950 to 1952, when pneumothorax was discontinued. Patient well and on full duties until 1954 when she developed a recurrent far-advanced ipsolateral lesion. Bronchial aspirate was positive for tubercle bacilli. Note very rapid clearing of the lesion within an interval of 5 weeks following the instillation of endobronchial INH. This patient was on concomitant oral INH and PAS in full doses, but in spite of this she developed a cavitational lesion 2 months following the complete regression of the original massive lesion. The cavity disappeared completely in 1½ months following a second endobronchial instillation. Note complete restitution to normal of the parenchyma except for the basal diffuse cloudiness which represents pleural thickening following the abondonment of the original pneumothorax.

drug has definitely proved its antituberculosis effect clinically. It has the advantage of low toxicity even when administered over a long period of time. With respect to strains resistent to SM it is more effective because of its ability to penetrate the cell membrane in effective concentration which is not true of SM.[10, 11] For example, a concentration of 0.05 gamma/ml. of INH will prevent the growth of H37Rv strains when compared with 25 gamma/ml. in the case of SM. This latter concentration is therapeutically not possible.

Resistance studies[8] indicate that most strains of the tubercle bacillus become resistant to INH in from two to four months, which probably accounts for the rather dramatic initial systemic as well as roentgen changes which taper off as the time of its use is increased. When combined with PAS, however, resistance is much longer in developing and much longer than when combined with SM. In the present study this combination was not used as it was the intent to study only one drug.

Following study of the various available preparations of INH, a lyophilized form manufactured by the Panray Corporation of New York was found most suitable. This preparation comes in sterile vials containing 1 gram of the drug. The addition of 20 cc. of sterile olive oil and shaking well resulted in the *basic suspension* used in this study. This suspension is easy to work with and readily instilled with the catheters and instruments devised. A 15 or larger gauge needle facilitates aspiration into a standard syringe. The *radiopaque suspension*, the use of which will be described later, is made by adding 10 cc. of sterile olive oil and 10 cc. of Dionosil to the 1 gram vial of INH.

Bronchographic and Bronchoscopic Observations on Behaviour of Oily Substances in the Lung

General observations in the use of oily contrast and therapeutic media in the lung indicate that such substances have little deleterious effect on the parenchyma (not true of mineral oils); and furthermore, that such preparations may remain safely in residence for many months as can be appreciated from the study of films following lipiodol bronchography. These media have the property of clinging to the bronchial mucosa by capillary attraction in thin films and readily enter the alveoli when used in excessive amounts; or when of low viscosity. Admixture of the basic suspension with Dionosil confirmed a parallel behaviour for this suspension. From these considerations it is assumed that such media will remain *in situ* long enough to be phagocytized and otherwise distributed throughout the lobe.

Retention of oily media in the lungs with anesthetized bronchi depends on the absence of the cough reflex and the suction action of inspiration which exceeds the expellent effort of expiration. This phenomenon is constantly seen in bronchography when the oily contrast medium is seen to make jerky progress towards the periphery of the lung with each inspiration. This inspiratory pull is quite forceful since it functions anti-gravitationally as can be seen when upper lobes fill when the catheter

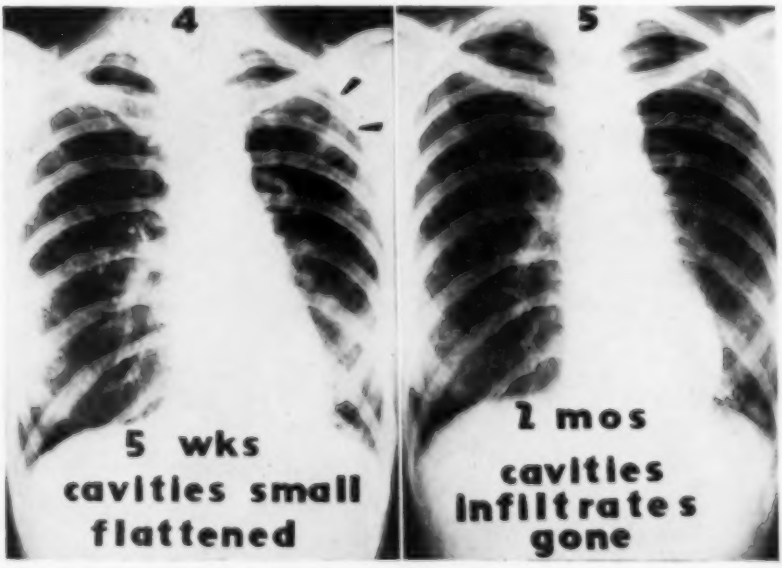
is juxtaposed at an upper lobe orifice even when the patient is erect. Bronchoscopically this retention is confirmed following introduction deep into a lobe, when prolonged waiting will not reveal the presence of the medium at the mouth of the orifice.

FIGURE 3: D. S., a white female, age 23, with positive bronchial aspirate and far-advanced bilateral lesions of the infiltrative and cavitational types. Patient acutely ill. In the serial x-rays note the specific lytic action of the INH endobronchial instillations on the lesions and the rapid restoration to normal tissue in a matter of weeks. (See view 4 & 5 on facing page.)

Lipoid granulomas following the instillation of peanut oil based contrast media have been reported.[15] Personal experience with similar media in 297 recorded five-lobe bronchograms and 70 penicillin (peanut oil base)[12] instillations would indicate, at least in the author's experience, that such incidence is comparatively rare. None were encountered in the above cases. In the present study 71 instillations were made with the basic suspension with no evidence of such granulomas. An excellent opportunity was present to detect them since all patients had weekly chest films taken following instillation and later at monthly intervals throughout the period of observation. In none of the series was there any indication of alien shadows which could be interpreted as granulomas.

Toxic Manifestations of INH Suspension

Preliminary studies with the basic suspension indicated that this medium was well tolerated by the parenchyma as well as the host with the exception of a transient pneumonitis which occurred soon after the introduction into the lobe. The typical reaction, as observed on x-ray film study, consisted of an over-all blurring when compared with the original film and a suggestion of a severe exudative process, which made one believe that the lesion had undergone a precipitous aggravation. With the exception of a slight pyrexia systemic reactions or symptoms did not occur. This process cleared rapidly within the space of one week but recurred following subsequent instillations though not to the same extent. No permanent effect on the parenchyma was noted. In the cases studied only one was considered severe, one moderately severe, and four slightly so. In the others no appreciable change could be detected.



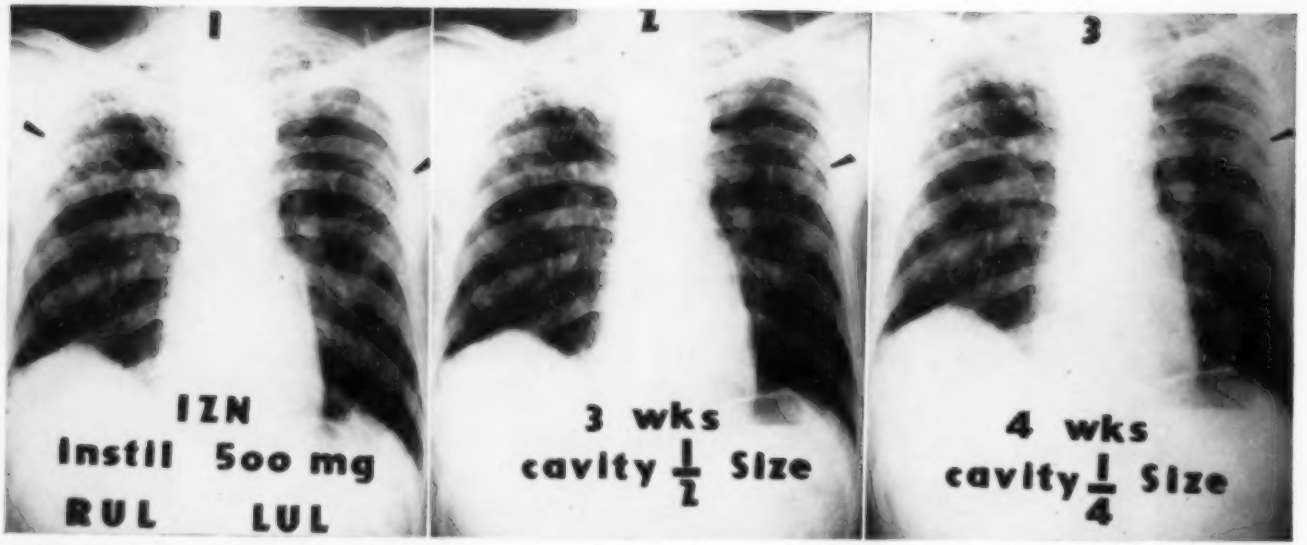


FIGURE 4: J. S., a white male, age 45, with a negative bronchial aspirate and bilateral far-advanced fibro-caseous lesions with a large cavity in LUL. History of recent sanatorium care for over 1 year on conventional therapy with INH, PAS, and SM. In the serial x-rays note the rapid decrease in the size of the cavity following 1 INH instillation as well as the resolution of the associated infiltrates. Cavity proper actually closed in 7 weeks. (See view 4 & 5 on facing page.)

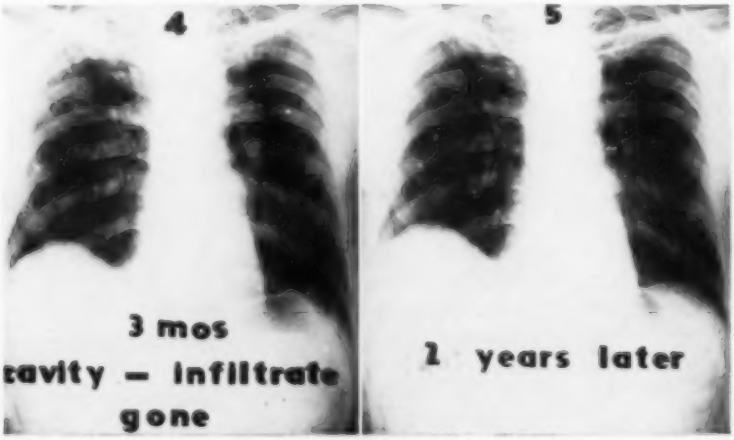
Clinical Material Used in the Study

The patients studied in this series were not selected but were treated as they appeared in sequence. All were ambulatory and only the more severely ill were confined to bed until the acute symptoms had subsided; but in no case longer than two weeks. They are classified on the basis of x-ray film findings and the severity of this involvement. All but two were on concomitant oral INH with conventional dosages. Two pregnancies, two diabetics and one far-advanced unilateral bronchiectasis were the non-tuberculous associated findings in the series. Two had complicating pleural effusion. In addition two had persistent cavities with pneumothorax failure. One had tuberculous bronchostenosis of the left side with a destroyed lung. Two were post-surgical positives—one a lobectomy with exudative spread and the other an ivalon sponge plombage. The others ranged from acute exudative to the chronic fibro-caseous and fibroid types though in some these phases were combined. Many cavities were encountered in the series—some single and others multiple in the same patient.

Technique of Secretion Studies

It was decided for the purpose of this study to use a refinement of the standard technique for the detection of the tubercle bacillus. This method yields a higher percentage of positives than is possible with the expectorate and reduces the number of false negatives. It has been the author's impression for some years that the usual sputum and gastric search for tubercle bacilli is rather coarse, tedious, and prone to many false negatives; furthermore a positive expectorate usually connotes fairly advanced disease and waiting for such a finding may make us temporize in specific therapy.

All the patients were bronchoscoped and the secretions obtained directly from the infected lobe or lobes by a special tubercle bacillus collector designed by the author.[17] All initial aspirates were studied by smear,



culture, and guinea pig inoculation whenever possible and the same was done when a persistent negative smear was obtained. The initial aspirate was generally sufficient for all three studies; though subsequent aspirates were found extremely scanty and frequently only a sufficient amount was obtained for a smear.

Technique of Laryngotracheobronchial Anesthesia

Proper anesthesia is a *sine qua non* as without it the procedure becomes a waste of time and effort. The cough reflex must be completely abolished not only in the involved bronchus but in all the others as well. The author has devised a method of anesthesia for bronchoscopy and bronchography which is safe and effective for these purposes[18] and has been used in all the patients of this series. Special attention must be paid in this technique, however, to spraying the trachea and lobar bronchi with an endobronchial atomizer prior to attempting the instillation of the basic suspension. It is wise to spray these structures and then wait about five minutes before instilling. If abundant secretions are present, it is necessary to completely aspirate the entire tracheobronchial tree as surface anesthesia is relatively ineffective in their presence.

Various Methods and the Instruments Used for the Instillation of INH Oily Suspension in the Lung

1. *Instillation with the Standard Bronchoscope*:

For instillation of the basic suspension into the lung bronchoscopically a new instrument had to be devised so that this could be done accurately and effectively. Since most of the lesions existed in the upper lobes, a problem arose when the standard bronchoscope was used. This instrument is generally best used for instillation purposes in the bronchial axis, when an ordinary metal catheter with a Luer-lok tip may be used. The designing of a special catheter made possible upper lobe instillation with little difficulty. This instrument consists of a monel tube of proper length whose tip was protected with a hollow ball and its terminal portion bent at an angle which was sufficient to permit passage through a 7 mm. lumen. Its proximal end was equipped with a Luer-lok adapter with a directional index bead in the plane of the curve. With this equipment the bronchoscope is placed opposite the upper lobe to be instilled and the patient's head and neck rotated to the opposite direction. The bronchoscope lip is then engaged in the lobar bronchus spur and the special catheter manipulated to enter the lobar bronchus which is now almost in the bronchoscopic axis. Care must be taken that the catheter end is not placed into a segmental bronchus which may then be filled to the exclusion of other diseased segments. This is particularly true of the anterior segment of the right upper and the lingular division of the left upper lobes. In practice, it is sufficient to introduce the suspension only into the lobar orifice as it will automatically be aspirated into the various segments of the lobe if the respiratory physiology is not too impaired. Accurate segmental localization is not necessary, except for

special reasons, since it is rather difficult to decide on x-ray observations alone how many segments are involved in a tuberculous process.

2. *Instillation with Special Optical Catheterizing Bronchoscope (Pentascope):* (Fig. 1)

A more accurate technique for instillation is with the use of an optical catheterizing bronchoscope designed by the author for this specific purpose. With this instrument it is possible to instil accurately into any lobar orifice under direct vision and even into segmental bronchi.

3. *Instillation by Bronchographic Technique:*

To extend this study for the benefit of those skilled in bronchography a technique of instillation has been worked out by the addition of Dionosil to the basic suspension which renders its adequately radiopaque. The

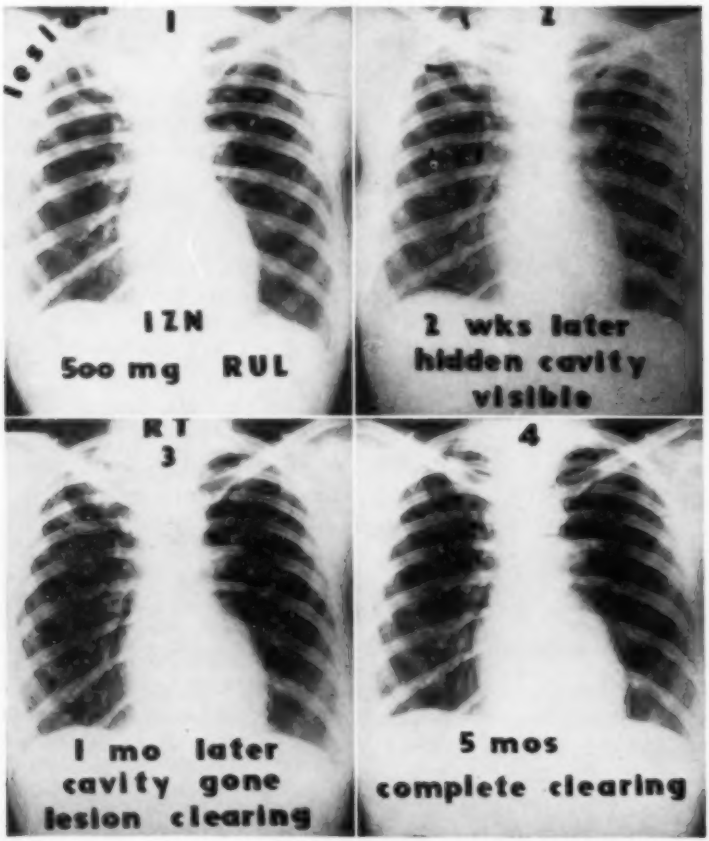


FIGURE 5: R. T., a white female, age 31, with positive bronchial aspirate. Note rapid clearing of the super-imposed tuberculous infiltrate revealing a hidden cavity. The cavity closed and the lesion almost completely regressed in 1 month. In 5 months there is complete clearing of the lesion with restoration to normal of parenchymal markings.

author prefers a bronchoscopic approach even when using this modified suspension for reasons of proper diagnosis, detection of obstructive or stenotic lesions, proper aspiration and adequate surface anesthesia; as well as for the progress detection of tubercle bacilli in the aspirate. The bronchographic catheter is introduced through the bronchoscope to the side desired and the latter withdrawn leaving the catheter in place. The catheter used for this purpose is a standard 12 F woven ureteral catheter, non-graduated, non-x-ray (C. R. Bard, Inc., Summit, New Jersey) (No. 302), which has been modified by the insertion of a snugly fitting two inch monel tube in the tip so that it occludes the second orifice. The tip over the metal tube is bent at an angle which still permits passage through a 7 mm. lumen bronchoscope. The proximal end was equipped with a special Luer-lok adapter and small tubular insert which prevents closure of the lumen when the adapter is tightened over a plastic or rubber tubular sleeve. The original length of the catheter is adequate for working over a fluoroscopic screen and the terminal curve and single aperture permit accurate localization of the suspension within the lobar orifice to be filled. Simple rotation at the carina permits easy shift from one main stem bronchus to the other. The terminal metal insert renders the tip constantly visible during fluoroscopy.

Lately it has been found advantageous to use the radiopaque suspension with all of the above techniques since hidden cavities and bronchiectatic areas become visible and obviate the use of tomography. An excellent film record can be obtained for verification of the degree and extent of filling. Another innovation has been the routine complete filling of all five lobes at the same sitting after the known diseased lobes have been filled. This takes care of latent or non-detectable infection in the other lobes and to date has not been found harmful.

No matter which of the above techniques is used instillation should be gentle, deliberate and slow. Most of the lobes will usually tolerate 10 ccs. of the suspension. It must be remembered that aspiration into the branch bronchi from the lobar bronchus takes some time and that flooding of the lobar bronchus too quickly will evoke a cough reflex no matter how adequate has been the surface anesthesia. The phenomenon may be explained by the pressure of air retained in the bronchioles and alveoli eliciting a distension cough reflex not controlled by the anesthesia.

Positioning of the Patient for Instillation

For bronchoscopic techniques instillation is originally made with the patient in the standard bronchoscopic position though immediately following this the patient is placed in more advantageous positions to take advantage of gravitational forces.

For upper lobe work the patient is placed in an oblique position with the side filled downward and the table inclined 5 or more degrees cephalad for about 15-20 minutes. For middle lobe the position is face down with the table in the horizontal position. For lower and lingular branch instillations the patient lies on his back with the table tilted 5 degrees

caudad. The Ritter electric hydraulic table with the modified head rest is excellent for these purposes as well as for general endoscopic work. Following the 15-20 minute rest, the patient is removed to bed or couch and the same position duplicated except for tilting. He is admonished not to cough. For multiple lobe filling a compromise position is arranged so that the flow will gravitate to the lobes filled. For example, when both upper lobes have been instilled the most favorable position will be flat on the back with the table tilted cephalad.

For five lobe filling with the bronchographic technique the patient lies on the radiographic table on his back. The more involved lobe or lobes are filled first by proper postural techniques. Oblique positioning to the right or left will almost completely fill the tracheobronchial tree of any particular side though a cephalad tilt while the patient is in this oblique position will take care of the upper lobes. The middle lobe fills best and spontaneously with the patient face downward with the table in the horizontal position. A good procedure to follow is to fill first the upper lobe with a tilt, the lower lobe with the table horizontal or tilted caudad. The same is then done with the other side. The patient is then placed on his face for automatic filling of the middle lobe. Experience will acquaint the operator with the time intervals needed for each side. Following instillation the patient rests on the radiographic table for 15-20 minutes prior to removal to bed or *cough*. It has been noted that once the suspension has penetrated the bronchioles and alveoli it remains there even after the cough reflex returns; though the patient still is exhorted not to cough.

Results

The results obtained in this study are summarized in Tables I, II and III. With respect to conversion, 86 per cent of the patients became and stayed negative during the period of observation. The shortest interval was 21 days and the longest 11 months. These figures, however, are not too accurate since the conversion interval was determined from the first positive to the first persistent negative; though in many cases bronchoscopic aspiration was not done until some time after the lesions had cleared or became stationary. The actual conversion time could have been much shorter. The average period of tabulated conversion was 96 days.

TABLE I
CONVERSION STUDIES WITH ENDOBRONCHIAL INH

No. Cases	18
No. Positive	14 (78 per cent)
Average Instil./pnt.	4 (500 mg. each)
No. Converted	12 (86 per cent)
Average Time for Conversion	96 (days)
Failures: Lobect., Plombage	2 (14 per cent)

TABLE II
X-RAY CHANGES FOLLOWING INH ENDOBRONCHIAL INSTILLATION

No. Cases	18
Average Instil./pnt.	4 (500 mg. each)
Complete Clearing	10 (59 per cent)
Exudate Clearing	14 (100 per cent)
Cavity Closure	10 (100 per cent)
Time to Clear/Close	55 days average
Time Remaining Static	14 months average
No Change: 2 Fibroid, 1 Plombage 1 Destroyed Lung	4 (22.2 per cent)

The x-ray film findings were rather striking with complete clearing of visible lesions in 10 of the series and complete closure in 10 separate patients with cavitation. Closure was effected in cases of single as well as multiple cavities. The time for clearing of the lesions as well as closure of the cavities was also remarkable with the shortest interval 14 days and the longest 120 days with an over-all average of 55 days. Complete clearing of the lesions was noted in 59 per cent of the series.

Weight gain varied from two to 29 lbs. The two diabetics, however, because of their dietary regimen lost six and 10 lbs. Two patients neither gained nor lost. With these exceptions the average weight gain distributed amongst the remaining 14 patients was 13 lbs.

The maximum sedimentation rate (MSR, Cutler technique) was usually proportional to the rate of clearing and systemic improvement. The greatest drop, prior to treatment, was 15 mm. and the lowest 0.5 mm. with the average of 6.0 mm. Following treatment the highest was 7.0 mm. (bronchiectatic case) and the lowest 0.5 mm. with an average of 2.2 mm.

An attempt was made to compare the findings in this pilot experiment with the gross results as obtained from a compilation of the figures found in the literature (Table III). Comparison is of course only relative because of the small number of cases in this pilot experiment. It will be noted

TABLE III
RESULTS OF PILOT STUDY COMPARED WITH AVERAGES IN THE LITERATURE*

	Literature Per Cent	Pilot Study Per Cent
Conversion	48	86
Gen. x-ray improv.	60	82.5
Exudate Clearing	24	100
Cavity Closure	30	100

*References 1 to 5

that the conversion rate is rather high (86 per cent); the x-ray improvement moderately higher (82.5 per cent); and the clearing of the exudates and cavity closure 100 per cent.

Discussion

It would seem from the results obtained in this pilot study that the theoretical considerations which made it possible were justified. Apparently the airways may be safely used as a portal of therapy with antituberculous agents in oily suspension and that the *concept of lobar or multilobar rather than body saturation* is a feasibility. It is also evident that to be effective the lobar physiology must not be too grossly impaired. With this type of therapy as well as with all others the need for early detection is still in order.

It is important to note the specific lytic action of the suspension on the tuberculous foci as seen on the serial x-ray films with the tendency to restoration to normal of the parenchyma. The onset of a transient INH pneumonitis should not be interpreted as an aggravation or failure of the procedure as following the apparent exacerbation, the foci begin to clear with disappearance of the exudates, visualization of hidden cavities, and reappearance of the parenchymal components. Cavity walls become better defined, thinner and the cavity itself soon becomes distorted or collapsed due to external pressure on its weakened walls; or it may diminish in size weekly with eventual complete closure. In the series complete disappearance of good-sized cavities usually occurred in six to seven weeks.

A question may arise on the relative value of the endobronchial therapy *per se* since it was combined with oral therapy of INH and PAS in many of the patients. An attempt was made originally to confine the therapy only to the endobronchial instillation and this was actually done in two of the patients by mutual consent; the others insisted in adjuvant therapy once the diagnosis of tuberculosis was made. These two patients (CS and JM) had excellent response with the endobronchial medication and cleared completely with only one instillation. One (J.S.) had been in a sanatorium for over one year on full doses of INH, PAS, and SM with a persistent large cavity. One endobronchial instillation closed the cavity in seven weeks. Several others of the series had complete regression of the lesions following a first instillation but had cavitational recurrences in different locations in spite of the fact that they were on continuous oral medication in full doses. A second instillation promptly resolved the lesions and there has been no further recurrence. Apparently oral medication in these particular patients was not effective in controlling or preventing recurrences of lesions.

From these observations it may be stated that the endobronchial therapy for pulmonary tuberculosis is indeed specific and apparently independent in its action from any effect of oral therapy.

The rapid disappearance of fluid in the two cases of effusion complicating the pulmonary lesions would indicate that this treatment is also effective against tuberculous effusions. Bronchoscopic observations with

respect to secretions show that these are considerably reduced in quantity and modified in character following INH instillation; and in many of the patients stopped completely within a short interval. Papanicoloau smears showed a rapid disappearance of the leukocytes with reversion to a normal cytogram.

Dosage schedules, because of the pilot nature of this study were more or less arbitrary and instillations were generally repeated when it was considered that an additional instillation would further effect the regression of the lesion. For the same reason accurate spacing could not be determined since the time intervals of effective change and quantitative response of the lesion were unknown factors. In general, it would now seem that from one to four instillations are necessary for maximum therapeutic effect spaced at 20 day intervals. This arrangement, however, is a mere guide and, if the lesions persist or recur, a second instillation is in order at any particular time.

The amount of the suspension used was generally 10 cc. per lobe and for these purposes the lingular division is considered as a separate lobe. Multiple instillations, when indicated, are made at the same time. With the five lobe bronchographic technique as much as 25-30 cc. of the radiopaque suspension may be used.

Resistance of the tubercle bacillus as judged clinically has not been a factor in this study when using the endobronchial instillation; though it may be expected when the scope of this technique is enlarged to a greater number of cases.

NOTES:

The INH preparation used in this series was the "Lyophilized Isoniazid 'Panray,'" which was kindly supplied for this study by the Panray Corporation, New York, New York.

All the bronchoscopic instruments mentioned as well as the optical catheterizing bronchoscope (Pentascope) and the special catheters are presently being manufactured by the George P. Pilling and Sons Company, Philadelphia, Pennsylvania, to whom the author has given originals which were personally designed and made.

SUMMARY

1. A series of 18 cases of pulmonary tuberculosis of various types and degrees of severity has been treated by the endobronchial instillation of an oily suspension of isonicotinic acid hydrazide as a pilot experiment.

2. This study would indicate that, with this new portal of therapy:
   a. The conversion rate becomes high and is obtained in rather short intervals.
   b. Complete disappearance of the lesion, its improvement and cavity closure incidence is higher and shorter in time intervals than with conventional oral therapy alone.
   c. INH in oily suspension endobronchially introduced has a pronounced specific lytic action on tuberculous foci.

3. The medication and the techniques described are safe and free from any detrimental parenchyma or constitutional effects.

4. The clinical and roentgen results appear to be permanent and not of short duration.

5. *Lobar or multilobar drug saturation* is proposed as a new concept in the chemotherapy of pulmonary tuberculosis.

RESUMEN

1. Como un experimento piloto, 18 casos de tuberculosis pulmonar en varias formas, se han tratado con instilaciones de una suspensión aceitosa de hidracida del ácido isonicotínico.

2. El estudio indicaría:

a. La proporción de conversiones se hace elevada y es obtenida a corto plazo.

b. La desaparición completa de la lesión, su mejoría y el cierre de cavidades es más elevada y se obtiene más pronto que el método oral.

c. INH (isoniacida liofilizada) en suspensión oleosa endobronquialmente tiene una acción lítica pronunciada en los focos tuberculosos.

3. La medicación y la técnica descritas son seguras e incapaces de dañar el parénquima y de causar daños al estado general.

4. Los resultados clínicos y radiológicos parecen ser permanentes y no de corta duración.

5. *La saturación lobar o multilobar* se propone como un concepto nuevo en la quimioterapia de la tuberculosis.

RESUME

1. A titre d'essai expérimental, une série de 18 cas de tuberculose pulmonaire de type et de gravités différentes a été traitée par instillation endobronchique d'une suspension huileuse d'hydrazide d'acide isonicotinique.

2. Cette étude indiquerait que, avec ce nouveau mode de traitement:

a) le taux de négativation est élevé, et est obtenu en un temps relativement court;

b) la disparition complète de la lésion, son amélioration et la fréquence de la fermeture cavitaire est plus élevée et survient dans un intervalle de temps plus court qu'avec le seul traitement buccal conventionnel.

c) L'INH (isoniazide lyophilisé) en suspension huileuse administré par voie endobronchique a une action lytique spécifique prononcée sur les foyers tuberculeux.

3. La médication et les techniques décrites sont sans effets secondaires nocifs sur le parenchyme ou sur l'état général.

4. Les résultats cliniques et radiologiques semblent être stables et de longue durée.

5. *La saturation médicamenteuse lobaire ou multilobaire* est proposée comme un nouveau procédé de la chimiothérapie de la tuberculose pulmonaire.

ZUSAMMENFASSUNG

1. Eine Reihe von 18 Fällen von Lungentuberkulose verschiedener Formen und Schweregrade wurde in einem Routineversuch mit endobronchialer Instillation einer öligen Aufschwemmung von INH behandelt.

2. Diese Untersuchung vermag zu zeigen, dass mit diesem neuen Zugang der Therapie:

a. Die Ziffer der Bazillenfreiheit gross und in ziemlich kurzem Zeitabschnitt erreicht wird.

2. Komplettes Verschwinden der Herde, ihre Besserung und das Vorkommen von Kavernenverschluss ist häufiger und erfolgt in kürzeren Zeiräumen als durch die übliche orale Therapie allein.

b. INH (lyophilisiertes INH) in öliger Aufschwemmung endobronchial eingeführt hat eine ausgepochene Lytische Wirkung auf tuberkulöse Herde.

3. Die beschriebene Verordnungsweise und Technik ist sicher und frei von irgendwelchen schädlichen Wirkungen auf Parenchym oder Konstitution.

4. Die klinischen und röntgenologischen Resultate scheinen anhaltend und nicht von kurzer Dauer zu sein.

5. Lobäre oder multilobäre Arzneimittelsättigung wird als ein neuer Begriff in der Chemotherpie der Lungentuberkulose vorgeschlagen.

REFERENCES

1 Silikoff, I. J. and Robitzek, E. H.: "Tuberculous Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid," *Dis. Chest*, 21:385, 1952.

2 Robitzek, E. H., Selikoff, I. J., Mamlok, E. and Tendlau, A.: "Isoniazid and Its Isopropyl Derivative in the Therapy of Tuberculosis in Humans: Comparative Therapeutic and Toxicological Properties," *Dis. Chest*, 22:1, 1953.

3 United States Public Health Service, Federal Security Agency: "Control Study of Comparative Efficiency of Isoniazid, SM-Isoniazid and SM-PAS in Pulmonary Tuberculosis Therapy," *Am. Rev. Tuberc.*, 67:108, 1953.

4 Salkin, D. and Schwartz, J. A.: "Roentgenological Changes of the Lung Associated with Isoniazid Therapy in Pulmonary Tuberculosis," *Dis. Chest*, 26:255, 1954.

5 Dooneief, A. S. and Hite, K. E.: "Indefinitely Prolonged Chemotherapy for Tuberculosis," *Am. Rev. Tuberc.*, 70:219, 1954.

6 Bormioli, R.: "Resultats de la Therapie Endo-bronchique avec L' I.A.I. dans Quelques Cas Particuliers de T.B.C. Pulmonaire Specifiquement Caverneuse," Transactions II International Congress of Bronchoesophagology, p. 150, 1953.

7 Bonarrigo, N.: "Bronchoscopy, Bronchoscopo-therapy, Bronchoscopic Aspiration and Endobronchial Instillations of Antibiotics in Pulmonary and Bronchial Tuberculosis," Transactions I International Congress of Bronchoesophagology, p. 73, 1952.

8 Sweany, H. C. and Dunbar, F. P.: "The Problem of Bacterial Resistance in Antimicrobial Therapy of Tuberculosis," *Dis. Chest*, 27:260, 1955.

9 Lemon, W. S.: "The Anatomical Factors Involved and the Mechanisms Employed in Removal of Minute Particles of Foreign Material from the Lungs: An Experimental Study," *Transactions of Assoc. Am. Phys.*, 53:278, 1937.

10 Machaness, G. B. and Smith, N.: "The Action of Isonicotinic Acid Hydrazide on Intracellular Tubercle Bacilli," *Am. Rev., Tuberc.*, 66:125, 1952.

11 Machaness, G. B. and Smith, N.: "The Bacteriocidal Action of Isoniazide, Streptomycin, and Terramycin on Extracellular and Intracellular Tubercle Bacilli," *Am. Rev. Tuberc.*, 67:322, 1953.

12 Carabelli, A. A.: "Acute Bronchopulmonary Suppuration: Therapy with Endoscopic Application of Oleaginous Pencillin," *Dis. Chest*, 25:316, 1954.

13 Miller, W. S.: "The Lung," Charles C Thomas, Baltimore, p. 3, 1937.

14 Porcellati, G. and Preziosi, P.: "Biological Transformation of Isonicotinic Acid Hydrazide," *Enzimologia*, 17:47, 1954. *Am. Rev. Tuberc.* (Abstracts), 73:64, 1956.

15 Storrs, R. P., McDonald, J. R. and Good, C. A.: "Lipoid Granuloma of the Lung following Bronchography with Iodized Oil," *J. Thoracic Surg.*, 18:561, 1949.

16 Sullivan, R. D., Barclay, R. K. and Karnofsky, D. A.: "Effects of High Doses of Isoniazid in Man," *Am. Rev. Tuberc.*, 69:957, 1954.

17 Carabelli, A. A.: "Endoscopic Collection of Neoplastic Cells and Tubercle Bacilli from the Bronchi," *Dis. Chest*, 18:98, 1950.

18 Carabelli, A. A.: "The Use of Pontocaine in Subposoligical Quantities for Bronchoscopy and Bronchography," *Anesthesiology*, 13:169, 1952.

SECTION ON CARDIOVASCULAR DISEASES

Patent Ductus Arteriosus in the Adult With Partial Reversal of Flow

PAUL WINCHELL, M.D., JAMES REDINGTON, M.D.
and RICHARD L. VARCO, M.D., F.C.C.P.*
Minneapolis, Minnesota

The clinical and physiological characteristics of the uncomplicated patent ductus arteriosus in the adult have been well-defined and understood for many years. A typical continuous murmur usually develops early in life; the electrocardiogram is usually normal or shows a left axis deviation; and heart fluoroscopy ordinarily shows only mild to moderate left ventricular enlargement, vigorous aortic pulsation, and increased pulmonary blood flow. In addition, cyanosis does not occur unless severe congestive cardiac failure develops in the terminal stages of the disease.[1]

In 1925, following a review of 16 atypical cases of patent ductus arteriosus in which right ventricular hypertrophy was present, it was pointed out that reversal of flow through the ductus arteriosus and the consequent development of lower extremity cyanosis and clubbing could and probably did occur in at least six of the patients studied.[2] Recently the syndrome of patent ductus arteriosus with pulmonary hypertension and reversal of flow through the ductus arteriosus has been well-described and documented in scattered reports.[3-6] The following cases are believed representative of that group.

Case Reports

Case 1: M. C., a 44 year old white woman entered the hospital for the first time on December 30, 1953. She gave a life-long history of dyspnea on effort and of becoming tired easily. As a child she had been "sickly" and never able to keep up with her playmates. Cyanosis on exertion was first noted in 1940 at the age of 30. Hemoptysis of approximately one-half cup of blood first occurred in 1947 and was subsequently followed by eight similar episodes over a period of four years. She had previously worked as a beauty shop operator but after 1946 was limited to manicure work because of weakness and dyspnea. There was no history of dyspnea at rest or of orthopnea. She noted hoarseness on several occasions.

She had been studied in hospitals for the first time in 1951 when she complained of severe dyspnea on exertion and could not walk over 20 feet without stopping to rest. On examination in 1951, she was noted to have cyanosis of the lips and fingers and marked cyanosis with definite clubbing of the toes. The blood pressure was right arm 108/92, left arm 112/90, right leg 140/94, and left leg 142/90 mm. Hg. The lungs were clear. The heart was generally enlarged. The pulmonary second sound was louder than the aortic second sound. A low-pitched diastolic murmur was heard in the fourth inter-

*From the Departments of Medicine and Surgery, University of Minnesota Medical School, University Hospitals.

TABLE I
CATHETERIZATION DATA—1953—CASE 1

Site of Blood Sample	Pressure Mm. Hg.	O_2 Content Vol. Per Cent	O_2 Saturation Per Cent
Pulmonary artery	85/60	18.4	63
Right atrium		18.0	62
Femoral artery	110/89	17.6	60
Brachial artery (left)	117/88	27.6	94

The pulmonary artery and systemic artery pressures were not recorded simultaneously, which may account for the considerable difference between them.

costal space to the left of the sternum. There was no peripheral edema. The hemoglobin was 21.1 gm./100 ml., the venous pressure 7.0 cm. of Na. citrate solution. The arm to tongue circulation time (decholin) was 36 seconds while the vital capacity was 88 per cent of normal. An electrocardiogram showed right axis deviation and right ventricular strain. Cardiac fluoroscopy showed considerable enlargement of the right ventricle and less marked enlargement of the left ventricle. The findings at cardiac catheterization are recorded on Table I. She was discharged with a probable diagnosis of Eisenmenger's complex.

During the next two and one-half years, she worked 15 to 30 hours weekly until late in 1953 when she re-entered the hospital because of increasing fatigue and dyspnea. On examination she was found to be a malnourished, chronically ill 44 year old woman with severe dyspnea on effort. The blood pressure was 100/60 mm. Hg. There was marked cyanosis and marked clubbing of the toes (Figure 1). The lungs were clear. The heart was generally enlarged with a diffuse maximal impulse over the fourth intercostal space to the left of the sternum. The pulmonary second sound was accentuated. A grade II blowing diastolic murmur was heard along the left sternal border radiating to the apex when the patient was in the left lateral decubitus position. A rough systolic murmur was heard intermittently at the base. There was no peripheral edema. The hemoglobin was 23.3 gm./100 ml. Electrocardiogram showed right ventricular preponderance and strain (Figure 2). Chest x-ray film (Figure 3)

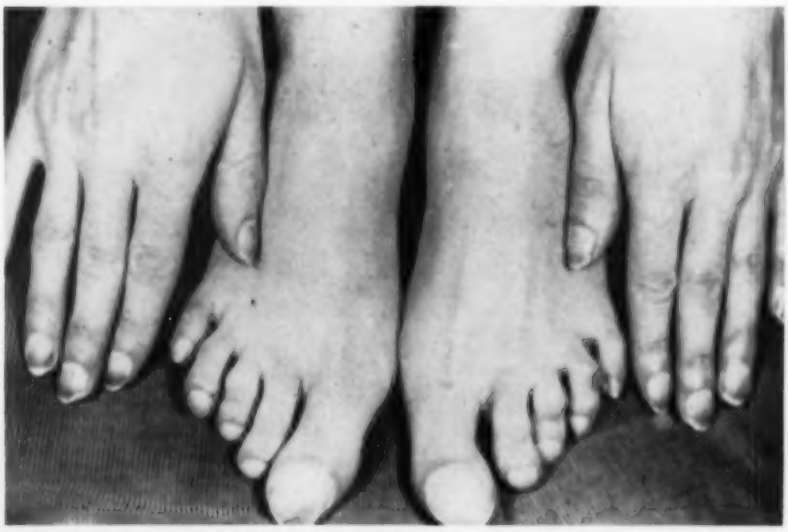


FIGURE 1: Photograph of hands and feet of Case 1 showing distinct clubbing of the toes without similar changes in the fingers.

TABLE II
EFFECTS OF BREATHING 100 PER CENT O_2 ON FEMORAL ARTERY SATURATION—CASE 1

	1951	1953
	Per Cent	Per Cent
Femoral saturation at rest	53	60
Femoral saturation after breathing 100 per cent O_2	74	69

In 1951, there was a considerable drop in the amount of desaturated pulmonary artery blood shunting into the aorta after breathing 100 per cent oxygen. Much less change was produced two years later under the same circumstances, suggesting that the pulmonary resistance was less altered by high oxygen tensions in the inspired air.

and cardiac fluoroscopy showed primarily right ventricular enlargement. The pulmonary arteries were enlarged but the peripheral pulmonary vessels were diminished in size. Arterial oxygen studies are recorded in Table II. A retrograde aortogram through the left brachial artery outlined the aorta with no evidence of coarctation. A slight outpocketing of the medial portion of the arch in the position where a ductus arteriosus is usually found was seen but there was no flow of dye from the aorta to the pulmonary artery. As a result of the studies it seemed likely that the patient had

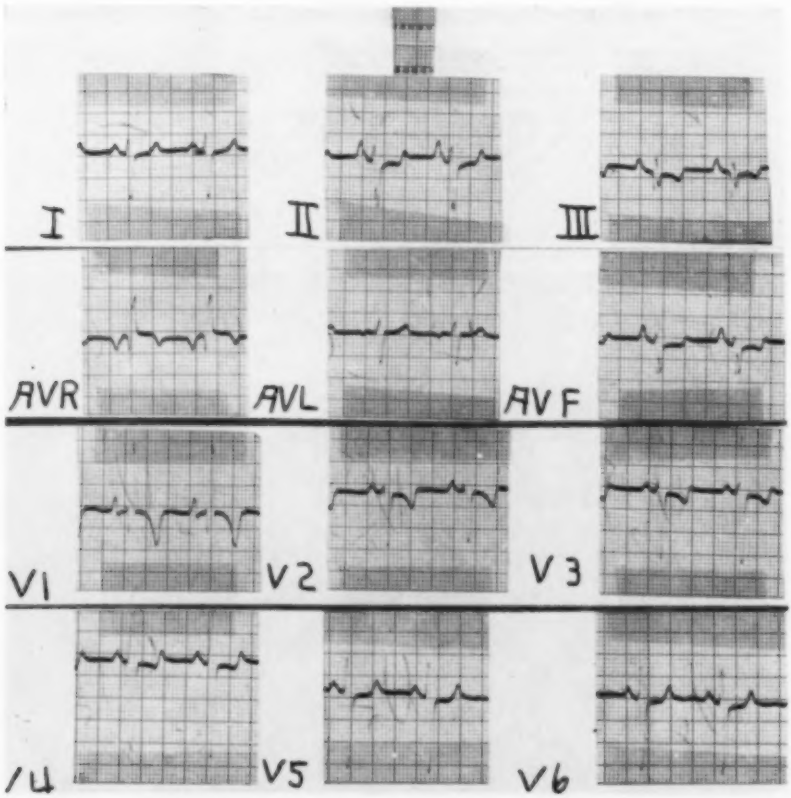


FIGURE 2: Electrocardiogram from Case 1, interpreted as showing marked right ventricular hypertrophy and strain, normal sinus rhythm.

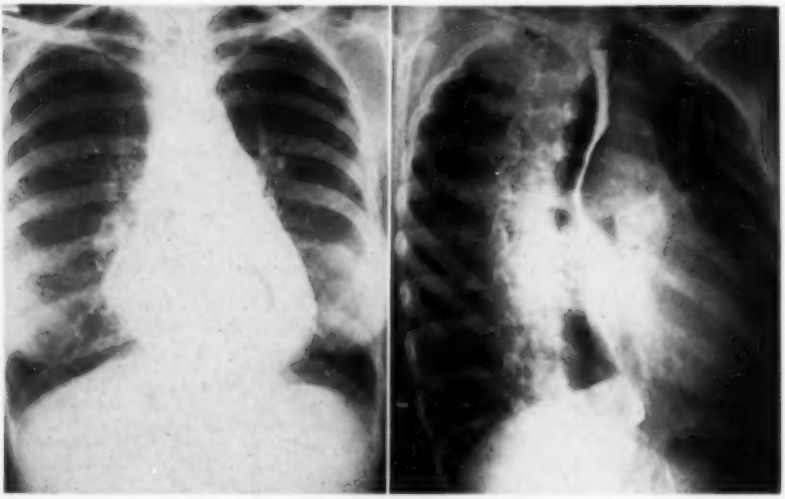


FIGURE 3: Posteroanterior and right-anterior oblique chest views of Case 1. Calcification in the ductus arteriosus is visible.

a patent ductus arteriosus with severe pulmonary hypertension and a shunt from pulmonary artery to the distal aorta, with no other apparent cardiac defects.

The seriousness of an operation was stressed for this patient. However, she desired to undergo any type of corrective surgery which might benefit her. While in the hospital she was a total invalid because of exertional dyspnea. The plan was to place a small diameter shunt between the pulmonary artery and the left atrium before cross clamping the ductus arteriosus. Then if the patient tolerated closure of the ductus

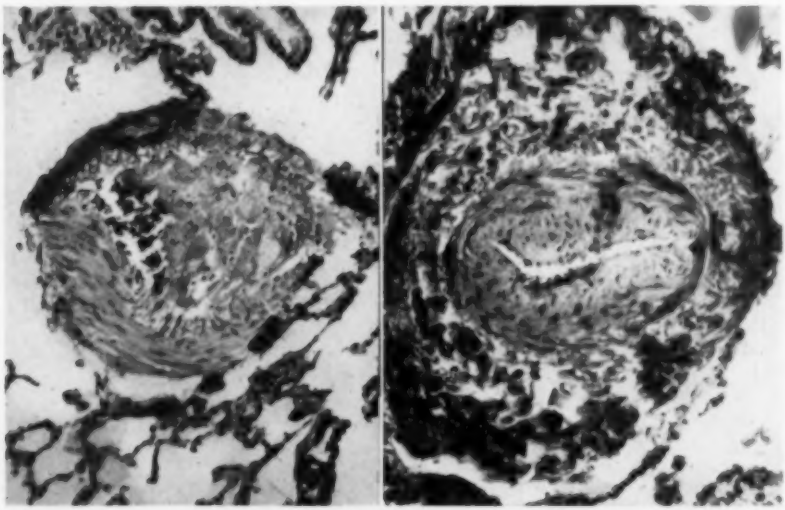


FIGURE 4 FIGURE 5

Figures 4 and *5:* Photomicrographs of small pulmonary arteries from Case. Striking intimal proliferation is present.

arteriosus it was to be divided and ligated. It was thought that this technique would decrease right heart work by decompressing any intolerable right ventricular pressures developing after the shunt through the ductus arteriosus had been eliminated. Moreover, it was hoped that this leak would contribute a volume flow adequate to sustain sufficient blood volume in the systemic circulation, especially the coronary arteries during an interval when the right heart was incapable of pumping enough blood through the arteriosclerotic pulmonary circuit. Perhaps with time for readjustment a regression of the lung lesions would follow. Once her clinical status had improved enough, at a second operation the arterial shunt between the pulmonary artery and the left atrium could then be disconnected. It was appreciated that such an anastomosis would result in mild generalized cyanosis rather than the regional cyanosis already present.

At operation the ductus arteriosus was estimated to have a diameter of 20 to 25 mm. It was thickened and contained calcium. There were evident thrombi in all branches of the right pulmonary artery with wide spread calcific deposits in the arterial wall. The proposed anastomosis of the left atrium to a branch of the pulmonary artery could not be carried out because of thromboses throughout the smaller pulmonary arteries. A tentative clamping of the ductus arteriosus was attempted to note the heart's tolerance of the altered hemodynamics. The cross clamping unfortunately eventuated promptly in ventricular fibrillation. A normal rhythm could not be reestablished despite recourse to a variety of resuscitative techniques.

At autopsy two areas of infarction were present in the upper lobe of the right lung. The right and left pulmonary artery branches were dilated and showed a marked degree of atherosclerosis. A laminated thrombus was present at the bifurcation of the right pulmonary artery and extended into the main lobar branches with complete occlusion of the opening to the upper lobe. The ductus arteriosus entered the aorta 2 cm. beyond the left subclavian ostium. The aorta in this area showed moderate atherosclerosis and was calcified. The left pulmonary artery was markedly atherosclerotic with calcification and sclerosis of the intimal layer. Marked plaque formation and ulceration of the intima were present in the left pulmonary artery where the ductus arteriosus entered. The right ventricle was hypertrophied and dilated, its walls measuring 1.2 cm. in thickness. The left ventricle measured 1.4 cm. in thickness. The valves were all normal. No other cardiac defect was present.

Microscopic examination of the lungs showed areas of atelectasis and infarction. The smaller pulmonary arteries showed striking changes, mainly of thickening due to intimal fibrosis with fragmentation and duplication of the elastic fibers (Figures 4 and 5). Vascular lesions in the form of small cavernous channels supported by connective

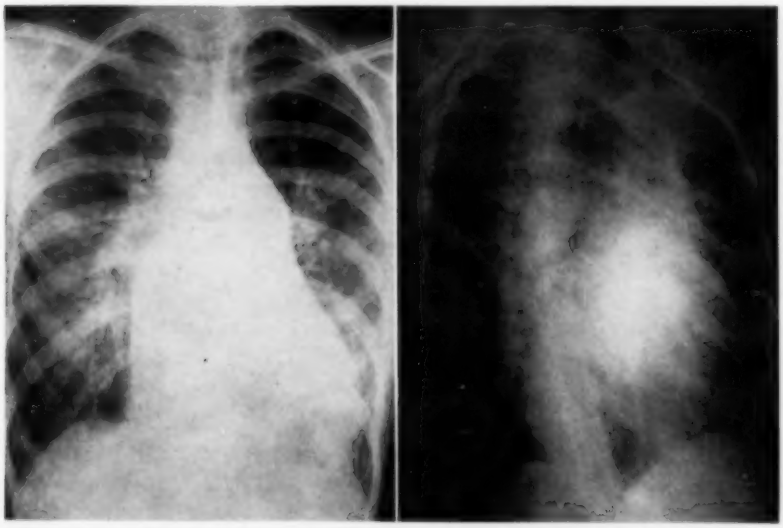


FIGURE 6: Chest views of Case 2. Enlargement of both ventricles and the pulmonary artery segment is present.

TABLE III
CARDIAC CATHETERIZATION DATA—CASE 2

Chamber	Pressure Mm. Hg.	O_2 Content Vol. Per Cent	O_2 Saturation Per Cent
PA	102/64	17.54	83
RV	100/ 7	13.21	63
RA	6	12.98	62
SVC		12.79	62
IVC		13.01	62
FA		19.66	92

tissue containing endothelial cells were present. Sections of the right pulmonary artery showed severe atherosclerotic changes with calicfication as well as a laminated thrombus.

Case 2: This patient was a 21 year old woman who gave a history of life-long inability to keep up with other people of her age. Her symptoms were primarily those of shortness of breath on effort. In addition, she had noted paroxysmal nocturnal dyspnea and ankle edema. She had never been cyanotic. Because of her cardiac symptoms she had been forced to discontinue school at an early age. There had been many episodes of respiratory tract infection and bronchitis. There was no antecedent history of rheumatic fever.

The physical examination at the time of her first hospital admission was negative except for the heart and for a palpable thyroid gland adenoma, which with her hyperactivity and a fine tremor led to the clinical diagnosis of thyrotoxicosis. The heart was not enlarged on physical examination. There was a grade III systolic murmur heard best along the left sternal border and at the apex. In addition, a grade I diastolic blowing murmur could be heard along the left sternal border. There was no cyanosis of either the mucus membranes, the finger nails, or the toe nails. The blood pressure was 118/74 mm. Hg.

The pertinent laboratory findings on the first hospital admission were as follows: The urine was within normal limits. The hemoglobin was 15.3 gms. and the white blood count was 6,600 with 49 per cent neutrophils, 42 per cent lymphocytes, 5 per cent monocytes, 3 per cent eosinophils, and 1 per cent basophil. The radioactive iodine uptake was 53 per cent of the administered dose at the end of 24 hours. An electrocardiogram showed atrial fibrillation at a slow rate. The frontal plane axis was about +80°. There were marked ST segment and T wave changes in leads II, III, AVF, and V5 and V6 suggestive of digitalis effect or possibly a left ventricular strain pattern. No evidence of right ventricular hypertrophy could be seen. Cardiac fluoroscopy showed marked enlargement of the heart which was thought to involve both the left and right ventricles. Mild left atrial enlargement was also observed in the left anterior oblique view. The pulmonary artery segment and the central and peripheral pulmonary arterial branches were considerably enlarged. The aorta was thought to be small (Figure 6). The findings were consistent with a left to right shunt and because of the slight but definite left atrial enlargement it was thought that either a ventricular septal defect or a patent ductus arteriosus would be the more likely possibility.

Cardiac catheterization was carried out and the significant findings are indicated in Table III. Despite severe pulmonary hypertension a considerable left to right shunt at the level of the pulmonary artery was found and was thought to be consistent with either patent ductus arteriosus or an aortic pulmonic window.

In view of the co-existing thyrotoxicosis it was thought advisable to control this portion of her illness first. Initial attempts using propylthiouracil were not effective and it was necessary eventually to administer relatively large doses of radioactive iodine. By February of 1956 she was somewhat hypothyroid, the radioactive iodine uptake being 6.6 per cent at 24 hours.

She was readmitted to hospital in February of 1956 for an attempt at corrective surgery. There had been little change in her symptomatology except that she had noted cyanosis with exercise on several different occasions. Her symptoms of nervousness were well controlled and her other symptoms directly referable to the cardiovascular system were unchanged despite the fact that she was then hypothyroid.

The physical examination at the time of her last admission showed the blood pressure to be 100/78 mm. Hg. The cardiac murmurs were unchanged. It was thought that distinct but mild cyanosis of the nail beds was present.

There were no significant changes in the laboratory studies other than in the arterial saturation. A femoral artery blood sample collected at rest showed the oxygen saturation to be only 83 per cent. In view of this finding simultaneous samples were taken from the right brachial artery and the left femoral artery in which the arterial saturations were 80 per cent and 88 per cent respectively. Since the brahcial artery saturation was lower than that of the femoral artery, it was thought that the diagnosis of aortic pulmonic window was more likely than that of patent ductus arteriosus with reversal of flow.

At the time of operation a diagnosis of patent ductus arteriosus was confirmed. A lung biopsy showed considerable medial hypertrophy and intimal proliferation in the small branches of the pulmonary artery. These findings were especially prominent in the arteries measuring under 100 micra in diameter where the arterial lumen was found to be nearly obliterated in several instances. This was thought to be grade III pulmonary arterial and arteriolar sclerosis. A corrective operation was not attempted at the time of exploratory thoracotomy.

The two cases described both presented the common complaint of progressively severe exertional dyspnea. Case 1 presented the more typical physical finding of regional cyanosis and clubbing limited to the lower extremities.[7] Variations of this sign have been reported since there may be retrograde flow of pulmonary artery blood into the left subclavian artery or even into the root of the aorta causing cyanosis of the upper portions of the body in general. This latter and more atypical physical finding was present in Case 2 at the time of her exploratory operation. The retrograde flow of desaturated pulmonary artery blood into the aortic root had been well demonstrated in one other instance.[8] The first case showed the usual findings of polycythemia, right ventricular hypertrophy on fluoroscopy, and a right ventricular strain pattern electrocardiographically with large pulmonary artery segments. In her case, a well calcified ductus arteriosus could also be seen and demonstrated on the x-ray films. Case 2 had apparently not been in a state of reversal long enough to result in the development of polycythemia. However, a regurgitant murmur of the Graham-Steell type was heard although the pulmonary systolic murmur was much the more prominent of the two.

That pulmonary hypertension may be progressive and that reversal of flow may occur relatively late in life, supporting the idea that the hypertension may be acquired rather than congenital, is demonstrated by the clinical course of Case 2.

It is generally agreed that the division of a ductus arteriosus when there is a significant (net) right to left shunt unless the patient is supported by some other procedure designed to maintain flow into the left ventricle is likely to prove fatal. One case in which the two circulations seemed to be "in-balance"—virtually equal pressures in aorta and pulmonary artery with bidirectional shunt and not truly continuous reversal of flow—has been operated on with survival of the patient. In this instance the ductus arteriosus was not completely divided and there have been no follow-up studies to determine if the communication has been completely closed.[9] The theoretical possibility exists that merely to divide such a "balanced" shunt, particularly in an adult, might do little to cure the existing pulmonary hypertension.

The effects on the pulmonary artery pressure of breathing 100 per cent oxygen have been well-studied and the chief result has been an inverse relationship between the oxygen tension of the inspired air and the pulmonary artery pressure.[8] In the presence of patent ductus arteriosus with reversal of blood flow the result should then be an increase in the saturation of femoral artery blood. It has been well-demonstrated that the opposite occurs when the O_2 content of the inspired air is reduced to a level of 10 to 14 per cent, the amount of the reduction in saturation ranging between 2.2 and 9.8 vol. per cent.[8] Whether or not these alterations occur in a given case would seem to depend on the degree of sclerosis of the small pulmonary artries and arterioles. In Case 1 the femoral artery saturation rose from 53 to 74 per cent in 1951 after breathing 100 per cent O_2 while a repeat similar study in 1954 showed a rise from only 60 to 69 per cent, suggesting the possibility that the pulmonary arteriosclerosis had progressed during the interval to the point that relatively little reduction in the pulmonary vascular resistance could accrue from the breathing of 100 per cent O_2 (Table II).

The basic reason why the adult with patent ductus arteriosus develops pulmonary hypertension and eventually reversal of flow is not entirely clear although the same problem exists in reference to other left to right shunts. Recent animal sudies may give a clue.

From the relationship:

$$\text{Pressure} = \text{Flow} \times \text{Resistance}$$

it is apparent that increases in pulmonary artery flow can result in increased pulmonary artery pressure provided the pulmonary vascular resistance remains constant or does not decrease excessively. That this does occur has been amply demonstrated by experience with the closure of atrial septal defects wherein distinct elevations of pressure in the pulmonary artery prior to operation are no longer present following closure of the defect and reduction of the pulmonary artery flow to normal. The highest pulmonary artery pressure we have observed to date with a simple atrial defect was 72/34 mm. Hg.—moderately severe pulmonary hypertension apparently based on increased flow alone but not enough to cause reversal of the shunt and cyanosis. Following closure of the defect, the right ventricular pressure was found to be 28/4 mm. Hg.—a normal value. There are scattered reports of moderate pulmonary hypertension in the presence of a patent ductus arteriosus reverting towards normal following surgery—from 100 mm. Hg. to 40 mm. Hg. in one case—apparently because the elevation in pressure originally depended almost entirely on increased pulmonary blood flow.[10] The same reduction occurs in certain instances following correction of ventricular septal defects.

A second aspect of the problem has to do with increased pulmonary vascular resistance resulting from increased pulmonary flow. In two series of experiments,[11,12] pulmonary hypertension has been consistently produced in dogs by the anastomosis of a systemic artery and a branch of the pulmonary artery. In each series marked changes in the pulmonary arteriolar structure occurred, including the appearance of medial muscular

hypertrophy and intimal fibrosis. Serial lung biopsies demonstrated the development of arteriolar medial muscular hypertrophy within a two-week period following the anastomosis, followed in turn by intimal fibrosis and and increase in the adventitial collagenous material over a two to three-month interval. No changes in alveoli, capillaries, or veins were noted.[12] The striking similarity of the changes to those noticed in humans with increased pulmonary vascular resistance has already been emphasized.[11] In some instances the smaller vessels are completely obliterated. That the size of the lumen in the pulmonary arteriole is the more important factor in determining pulmonary vascular resistance than is the increased viscosity of blood relative to polycythemia or other similar factors has also been demonstrated.[13]

It was further observed that the total amount of increase in pulmonary blood flow was not the sole factor in initiating the changes subsequently observed in pulmonary arteriolar structure and in pulmonary artery pressure. The type of anastomosis formed—whether end-to-end or side-to-side—was contributory in some way, the end-to-end anastomosis resulting in the greater amount of change. It has been suggested that the pulse wave form is of some significance and that the pulsatile thrust of blood into the pulmonary circuit is responsible in part for the changes observed.[12] Whether or not this is an important factor in the human cannot as yet be determined. The usual patent ductus arteriosus and aortic-pulmonic window function as side-to-side anastomoses in which the shunt is not obligatory. In the adult, for the former, the development of severe degrees of pulmonary hypertension is uncommon. A large ventricular septal defect approaching functionally a single ventricle probably more closely simulates the situation in the experimental animal and here marked pulmonary hypertension is necessary for survival, provided that pulmonary stenosis is not present. Simple atrial septal defects seem not to be ordinarily accompanied by severe pulmonary hypertension whereas atrioventricularis communis defects seem commonly to have marked elevations in pulmonary artery pressure. These are impressions not as yet statistically proved. They would suggest, however, that the presence of a large, pulsatile thrust through an obligatory shunt may be related to the development of the severe forms of pulmonary hypertension. The ordinary Blalock anastomosis does not duplicate this experimental situation. There are rare instances in which end-to-end anastomoses have been made in the adult between a systemic artery and the right or left pulmonary artery but none of these have had post-operative studies that would shed any light on this particular problem.

From the evidence at hand it would seem that a reasonable working hypothesis can be formulated to explain the course of events in the adult who develops pulmonary hypertension in the presence of a left-to-right shunt. It is known that increased pulmonary flow may in itself produce pulmonary hypertension and it is suggested that this in turn leads to anatomical changes within the small pulmonary arteries resulting in an increased pulmonary vascular resistance and with it a further aggravation

of the pulmonary hypertension. The presence of a pulsatile thrust of blood into the pulmonary circuit may also be of great importance.

One interesting question concerns whether or not these changes observed in the pulmonary arteriole in the severe types of pulmonary hypertension are reversible. It is not known if such regression occurs in man. The experimental preparation does show a regression of the anatomical changes in the pulmonary arteriole following correction of the systemic artery-pulmonary artery anastomosis. These changes occur very slowly over a prolonged period of time and in no animal thus far have the pulmonary arterioles returned entirely to normal.[11] The possibility of such regression occurring in man seems good enough to warrant further attempts at repairing surgically the patent ductus arteriosus in which reversal of flow has occurred.

The mechanism of death in the first case described, and in some others, has been ventricular fibrillation. It seems reasonable to assume that with obliteration of the ductus arteriosus and because of markedly increased pulmonary vascular resistance, the right ventricle is unable to maintain enough flow through the lungs and into the coronary circulation to perfuse adequately the myocardium. Under such circumstances ventricular fibrillation may easily occur. This constitutes a major problem that must be solved before the repair of this anomaly will become possible.

SUMMARY

1. Two examples of patent ductus arteriosus with pulmonary hypertension, reversal of flow, and cyanosis occurring in adults are described.

2. In Case 1 changes in the response to breathing 100 per cent O_2, as determined by studies of femoral oxygen saturations, suggest that the pulmonary vascular resistance became "fixed" as the disease progressed.

3. Clinical and experimental observations demonstrated that increased pulmonary blood flow results in pulmonary hypertension that may in turn be followed by pulmonary arteriolar, medial, and intimal thickening and increasing pulmonary vascular resistance. This is especially true if the flow is of the pulsatile type.

4. The pulmonary arteriolar changes in the experimental animal are but partially reversed during reasonable intervals of observation once the pulmonary pressure has been restored to approximately normal values.

5. For surgery to be successful in cases with marked reversal of flow some mechanism for maintaining adequate coronary flow and preventing ventricular fibrillation will be required.

RESUMEN

1. Se describen dos casos de conducto arterioso presistente con hipertensión pulmonar, inversión de la corriente y cianosis en adultos.

2. En el caso l, los cambois en la respuesta a respirar 100 por ciento, como se pudo determinar por los estudios de la saturación de oxígeno

femoral, sugieren que la resistencia pulmonar vascular se volvió "fija" al progresar la enfermedad.

3. Las observaciones clínicas y experimentales demonstraron que el aumento del flujo sanguíneo pulomar da por resultado la hiperstensión pulmonar que a su vez puede ser seguida por engrosamiento de la íntima arterional, así como engrosa miento de la media, y un aumento de la resistencia pulmonar. Esto es especialmente cierto si el flujo es de tipo pulsátil.

4. Los cambios pulmonares arteriolares en el animal de experimentación, sólo son parcialmente invertidos durante intervalos razonables de la observación una vez la presión pulmonar se ha restablecido aproximadamente a los valores normales.

5. Para que la cirugía tenga buen resultado en casos con marcada inversión del flujo se requerirá algún mecanismo para mantener el flujo coronario adecuado y para prevenir la fibrilación ventricular.

RESUME

1. Les auteurs décrivent leux exemples de persistance du trou de Botal avec hypertension pulmonaire, inversion du courant sanguin, et cyanose apparus chez des adultes.

2. Les altérations du cas I apparaissant lors de l'épreuve de la respiration à 100%, déterminée par l'étude de la saturation oxygénée de l'artère fémorale, donnent à penser que la résistance des vaisseaux pulmonaires s'était "fixée" alors que l'affection continuait sa progression.

3. Des observations cliniques et expérimentales ont démontré que l'augmentation de la circulation sanguine pulmonaire dépend de l'hypertension pulmonaire qui à son tour peut être suivie par un épaississement de la média et de l'intima des artérioles pulmonaires entrainant un accroissement de la résistance vasculaire pulmonaire. Ceci est particulièrement vrai si le débit est du type pulsatile.

4. Les altérations artériolaires pulmonaires chez les animaux d'expérience ne sont que partiellement réversibles pendant des intervalles raisonnables d'observation une fois que la pression pulmonaire est revenue à son taux approximativement normal.

5. Pour mener à bien les interventions dans les cas avec trouble marqué du débit, on doit arriver à maintenir un débit coronaire convenable, et prévenir la fibrillation ventriculaire.

ZUSAMMENFASSUNG

1. Es werden zwei Beispliele beschrieben von offenem ductus arteriosus mit pulmonalem Hochdruck, umgekehrter Strömungsrichtung und cyanose bei Ewachsenen.

2. Der Wechsel von 100% in der Antwort von Fall I bei der Atmung, wie aus Untersuchungen bei der Prüfung von femoralen Sauerstoffsättigungen hervorging, lässt vermuten, dass der pulmonale Gefässwiderstand zu einem "fixierten" wurde in dem Masse, wie sich die Krankheit weiter entwickelte.

3. Durch klinische und experimentelle Beobachtungen wurde nachgewiesen, dass eine erhöhte pulmonale Durchströmung eine pulmonale Hypertension zur Folge hat, die ihrerseits gefolgt sein kann von einer pulmonalen arteriolären Media-Intema-Verdickung und erhöhtem pulmonalem Gefässwiderstand. Dies ist besonders dann der Fall, wenn die Durchströmung vom pulsierenden Typ ist.

4. Die Veränderungen an den pulmonalen Arteriolen im Tierversuch lassen sich jedoch wenigstens teilweise wieder aufheben innerhalb übersehbarer Beobachtungszeiträume, wenn der pulmonale Druck erst einmal wieder auf annähernd normale Werte eingestellt ist.

5. Damit ein operativer Eingriff zum Erfolg führt in Fällen mit ausgesprochener Umkehr der Durchströmung, sind eine Reihe von Vorkehrungen zur Aufvechterhaltung einer ausreichenden coronaren Durchströmung und Vermeidung von Kammerflimmern erforderlich.

REFERENCES

1 Gross, R. E.: "The Patent Ductus Arteriosus. Observations on the Diagnosis and Therapy in 525 Surgically Treated Cases," *Am. J. Med.*, 12:472, 1952.

2 Holman, E.: "Certain Types of Congenital Heart Disease Interpreted as Intracardiac Arteriovenous and Venoarterial Fistulae. 1. Patent Ductus Arteriosus," *Bull. Johns Hopkins Hosp.*, 36:61, 1925.

3 Johnson, R. E., Wermer, P., Kuschner, M. and Cournand, A.: "Intermittent Reversal of Flow in a Case of Patent Ductus Arteriosus. A Physiologic Study with Anatomic Findings," *Circulation*, 1:1293, 1950.

4 Hultgren, H., Selzer, A., Purdy, A. and Gerbode, F.: "The Syndrome of Patent Ductus Arteriosus with Pulmonary Hypertension," *Circulation*, 8:15, 1953.

5 Dammann, J. F., Jr., Berthrong, M. and Bing, R. J.: "Reverse Ductus. A Presentation of the Syndrome of Patency of the Ductus Arteriosus with Pulmonary Hypertension and a Shunting of Blood from Pulmonary Artery to Aorta," *Bull. Johns Hopkins Hosp.*, 92:128, 1953.

6 Lukas, D. S., Araujo, J. and Steinberg, I.: "The Syndrome of Patent Ductus Arteriosus with Reversal of Flow," *Am. J. Med.*, 17:298, 1954.

7 Bothwell, T. H., VanLingen, B., Whidborne, J., Kaye, J., McGregor, M. and Elliott, G. A.: "Patent Ductus Arteriosus with Partial Reversal of the Shunt," *Amer. Heart J.*, 44:360, 1952.

8 Burchell, H. B., Swan, H. J. C. and Wood, E. H.: "Demonstration of Differential Effects on Pulmonary and Systemic Arterial Pressure by Variation of Oxygen Content of Inspired Air in Patients with Patent Ductus Arteriosus and Pulmonary Hypertension," *Circulation*, 8:681, 1953.

9 Kattus, A. A. and Muller, W. H., Jr.: "Patent Ductus Arteriosus with Reversal of Blood Flow. Report of a Successful Closure and Physiological Studies," *Ann. Surg.*, 138:870, 1953.

10 Adams, F. H.: "Pulmonary Hypertension in Children Due to Congenital Heart Disease," *J. Pediatrics*, 40:42, 1952.

11 Muller, W. H., Jr., Dammann, J. F., Jr. and Head, W. H., Jr.: "Changes in the Pulmonary Vessels Produced by Experimental Pulmonary Hypertension," *Surgery*, 34:363, 1953.

12 Ferguson, D. J. and Varco, R. L.: "The Relation of Blood Pressure and Flow to the Development and Regression of Experimentally Induced Pulmonary Arteriosclerosis," *Circulation Research*, 8:152, 1955.

13 Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T. and Hellems, H. K.: "Studies of the Pulmonary Circulation in Man at Rest. Normal Variations and the Interrelations Between Increased Pulmonary Blood Flow, Elevated Pulmonary Arterial Pressures and High Pulmonary 'Capillary' Pressures," *J. Clin. Investigation*, 26:561, 1950.

14 Ferguson, D. J., Berkas, E. M. and Varco, R. L.: "Process of Healing in Experimental Pulmonary Arteriosclerosis," *Proc. Soc. Exp. Biol. Med.*, 89:492, 1955.

Noises Heard at a Distance from the Chest

Second Series*

WILLIAM BENNETT BEAN, M.D., F.C.C.P.**
Iowa City, Iowa

"The abnormal murmurs, as well as the natural sounds of the heart are heard to a greater distance in proportion to their mere loudness, and that not only in the direction to which the current of the blood conducts them, but in all directions." —*Latham*

We are gathered on this occasion of physical and mental refreshment to do honor to the memory of Louis Mark who is no longer among us. In this materialistic age, we are self-conscious about anything which smacks of hero worship. Too often we forget our illustrious forebears and our cherished friends. Of all the professions, medicine leans most heavily on the past and loses most when it fails to remember its heritage. I hope my words tonight would have pleased Louis Mark, whose personality and contributions to chest disease did not prevent an enjoyment of fun in matters most austere and serious.

Once every second at least, four thousand times or more an hour, a hundred thousand times a day, sleeping and waking, active and quiet, heedful and heedless, our heart beats out its irrevocable time. Our pulse, a living pendulum of life, tells for us all the seconds, minutes, and hours that will never return. Who has not wondered at the long procession of these heartbeats on the ineluctible abscissa of time. This silent measure of the tides of life seem tireless as well as timeless. But upon occasions its quiet may be interrupted by strange sounds, sounds so loud that they escape the little sonic barrier of the chest. The beats become ominously loud. The uproar may grow insistent. Sometimes it gets amazed attention from the person who is making the loud noises and anyone else within hearing range. I wish to deal this evening with such noises as they have occurred in my own experience and in reports which I have gathered from a variety of physicians and medical writings. This topic is one of my avocations in medicine. It illustrates the ancient dictum that rare things teach us truth about commonplace things; and that what begins off the the beaten path may become a royal road of interest.

Some 15 years ago I began the curious hobby of collecting references to precordial noises heard by the unaided ear at a distance from the chest. I was on the lookout for examples. I found them. Indeed, my first interest was aroused by hearing such a noise. Four years ago, I used this collection as the basis of the Roger Morris lecture in Cincinnati. Later

*The Second Annual Louis Mark Memorial Address, presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

**From the Department of Medicine of the College of Medicine and the University Hospitals, State University of Iowa.

it was published.[1] I was hardly prepared for the deluge of letters, phone calls, and reprints which descended upon me. Apparently I had poached on the hobby of many physicians. Some chided me for failing to mention their paper. One was annoyed somehow that I had not included his favorite case, though he had neglected to publish it. Getting into that important medical journal, *Time*, produced the usual response of people with ticking ears, barking chests and such like, including a frantic Sunday call from a banker in South America whose ear ticked like a watch, though I could not identify it over the phone. Apparently it confused him when he tried to count his money.

I omit the embarrassing borborygmi of the dowager, famed in story and limerick, the infinitely varied sounds of wind from belches or escaping flatus, the 'tic'-tick of audible clicks in the ear, nose and throat which others as well as the unhappy victim may hear when intratympanic, palatine or eustachean tube muscles twitch after the manner of muscles about the eye when one is tired; and I omit also even the fleeting cry of the unborn babe in utero protesting rude expulsion into the outer world, the *vagitatus uterinus* which haunts the hearers. Omitting these and other unlikely sounds, the patient or physician may be startled by noises emanating from the chest produced by action of the heart and heard at a distance by the unaided ear.

Ancient medical records have no references to such sounds. The Bible has no precordial companion for the abdominal rumblings of Isaiah "whose bowels sound like an harp." There is no thoracic counterpart of the borborygmal chorus of Aristophanes' "Clouds." Only with the perfection of the art and science of physical diagnosis was an interest in normal pulmonary and cardiac sounds and noises developed sufficiently to recognize abnormal sounds.

Chest and Mediastinum

Dr. Richard Asher of London sent me the story told by his former chief, the late Dr. Theodore Thompson who had a patient with a large chronic hydropneumothorax.[2] He was a sturdy fellow and a keen huntsman. He continued to follow the hounds, for he never let his trouble become a disability. On occasions when his horse jumped a hedge and brook, members of the hunt in close pursuit thought that he had landed in the water because of the great roaring splash. To their astonishment, he would go galloping on unharmed, leaving the hunt in consternation. The noise was merely the splashing of his hydropneumothorax.

Traumatic pneumothorax must surely have produced loud noises in ancient wars and accidents. Medical reports go back a mere hundred years when Bricheteau[3] described such noises after crushing injury to the chest. The *bruit de moulin* — the noise of a mill wheel, happily combines the rhythmic splashing and the background throb of the wooden machinery. Captain Rees and Hughes[4] in the British Army in World War I rediscovered the sign and called it pericardial knock. Their report prompted Henley Munden[5] to record a mischance of sport and the risks

of rabbiting in this note. "I was called to see a boy who had been accidentally shot in the head and left side of the chest when rabbiting. About an hour before he died a loud cardiac 'click' developed which was synchronous with the heart systole and could be heard distinctly six or eight feet away. It bore no relation to the respiratory movements, as the respiration was Cheyne-Stokes in character and the sound persisted during the period of aponea. The click in the ear-piece of a telephone when the lever is raised illustrates it very well. During the last fifteen minutes of life the heart became very feeble and irregular and the 'click' disappeared."

Spontaneous and Induced Pneumothorax

Pneumothorax is a common cause of loud noises. Readers of Thomas Mann's *Magic Mountain* will recall his vivid description of the noises of pneumothorax. Fourteen new records, mostly from personal letters, indicate its frequency. Scadding and Wood[6] reported a case which probably holds the indoor record for loudness. They told of a young man in perfect health who had a 'sharp pain in the chest, and this was followed by an extremely loud peculiar noise accompanying the heart beat. The noise was so loud that it could be heard in the room below.' Three weeks later it disappeared without complication, despite the diagnosis of rupture of a heart valve.

Interstitial Emphysema of Lung and Mediastinum

I had the great good fortune to observe one of Louis Hamman's[5] early patients with interstitial emphysema, though there were no distantly heard sounds. One patient he described as follows: "A 51-year-old physician had pain in the chest while shaving. On the following evening of the next day while 'lying upon his left side, he heard a curious loud, bubbling sound with each contraction of the heart. His wife sitting upon the bed beside him could hear it very plainly.'"

A number of case reports mention loud murmurs as well as the more usual sounds heard only with the stethoscope. Pinckney[5] reported:

> A 24 year old white woman who had six different attacks of spontaneous pneumothorax, in some of which there was interstitial emphysema. On her third attack she had dull pain and dyspnea. "She also noted a loud, clicking, snapping noise audible at all times no matter what position she assumed. In addition when lying on the left side she heard another sound, a crunching, crackling sound like small chicken bones being crushed. This sound she cannot say with certainty was synchronous with her heart beat. Both sounds were easily audible to persons in the room with her." On her fourth attack three months later, pain developed while she was walking. Several hours afterward there was a loud clicking noise, and a crunching sound became audible. Roentgenograms showed a small pneumothorax on the left side. With her fifth attack 15 months later, she had only a heavy sensation. "Again the very loud clicking noise, synchronous with each heart beat, was easily audible to anyone within twenty or more feet, and slightly less audible was the crunching noise when she sat leaning forward on her left side." This lasted for six weeks, during which time her lung reexpanded.

Alimentary Canal

Recently I found Curtin's[9] report of cardio-esophageal gush and click. He reported three cases. In one, the story is as follows:

In 1894, a girl, nineteen years old, called at my office, saying that she had a queer noise which a doctor had told her was a heart murmur that he could hear without applying the ear to the chest. She informed me that it was not so loud that day, for she could not hear it. I listened to her chest and found a mild, double, mitral murmur, with evidence of some hypertrophy. She then complained of dyspeptic symptoms only. I told her to return to me if the sound came back, which she did next day. I could then hear a sound with the action of the heart, which was then excited; and, on withdrawing my ear one yard from the chest, I could hear a sound, which was before or early in the systole, when her mouth was open. When she closed her mouth the sound was very perceptibly deadened. It continued when her breath was held. On applying the ear to the chest the sound was subdued, being less distinct than when the ear was held in front of the open mouth. It sounded like a short gush of air from the throat modified by the upper air passages, giving it a low-pitched, grunting sound. I could get no sound at the epigastrium and there was no apparent effort of the diaphragm or abdominal walls as if expelling flatus from the stomach. The sound continued while she was talking and breathing. It did not appear to be a moan or grunt like a regurgitation of air from the stomach.

I gave her some potassium bromide, tincture of nux vomica, and compound tincture of cardamon and mint water. She called next day and I found that the heart had quieted down and the sound promptly disappeared.

Dr. Lewis January[10] called to my attention a rare instance of a healthy young man whose heart sounds were clearly audible several inches from his mouth when it was held open. He had no heart disease. X-ray study of the chest, esophagus, and upper gastrointestinal tract showed them to be normal. Perhaps some anatomic quirk permitted his esophagus to be patulous when his mouth was open and to act as a megaphone.

I offer an autobiographical note: Occasionally, when my stomach contains just the proper quantity of fluid and air, a happy postprandial mixture, and when semirecumbent in an easy chair, a systolic tinkle or splash is clearly audible to me and very diverting. It has been heard by others a foot away. The cardiac impulse on the diaphragm and stomach obviously produces the sound. It generally vanishes after a few minutes or can be eliminated by belching; but swallowing air or air and water has not brought it back at will.

Greene,[11] Allan[12] and others have reported similar cases. Occasionally in Machella's splenic flexure syndrome gas in a high riding colon may provide a drum on which the heart may beat away merrily through the diaphragm. Several hundred years ago Nicolas Tulp[13] had this strange tale of a reverberating spleen to tell:

Nothing in medical art is better known than that the spleen pulsates continually, if violently moved by the arteries. But for this organ itself to strike the ribs so forcibly that the sound of the beating (lit. flogging, or whipping) may be heard from afar, that certainly is novel, and perchance hitherto unheard of.

In the case of Nicolaus Fabrus, an active man, but rather frequently afflicted with black bile, a hardened (indurated) spleen made so forceful an impulse on the adjacent ribs, that not only he himself felt pain therefrom, but persons at a considerable distance might clearly hear the sound of the beats; and even so distinctly that one might count the separate impulses, and with the close-pressed hand feel the throb of the beating spleen.

In fact, I remember that in company with Henricus Saulius, the physician of Utrecht, I heard these repeated sounds at a distance of above thirty paces.

Pneumoperitoneum. In my original paper, I had not found any example of pneumoperitoneum associated with sounds heard at a distance. Since that time, I have the record of the following patient whose noises caused her much amusement. Dr. Fisher[14] of Providence, Rhode Island, related to me the following facts:

The patient was a 26 year old housewife seen first on the 30th of October, 1949, highly amused because of a clicking noise which occurred in her chest when she sat up. When she awoke at 2 a.m. to feed her infant son, she was suddenly aware of some pain between the shoulders and heard the clicking sound. Lying at an angle of 45° or less, the sound became inaudible. No abnormality could be found except that her heart made a sound like striking a ping-pong ball with a racket or clicking a telephone receiver, whenever she sat upright. After the first symptom, there were no further sensations. On fluoroscopic examination, air was noted beneath both sides of the diaphragm. There was no pleural or pericardial effusion. After three or four days, the noise disappeared completely. She remained subjectively well through the whole episode. The air got into her peritoneum in this wise. Her third child had been born three weeks previously. After a few days in the hospital and a few more days of rest at home she was up and about. Her obstetrician had suggested that she perform knee-chest exercises two or three times a day. She was not only athletic and very sturdily built, but had a proper New England conscience, so that she faithfully performed these exercises with great vigor. With the violence of her exercise and a patent cervix, she had achieved a do-it-yourself Rubin's test and introduced air into the peritoneum. I need not stress the lesson this bears for women in the postpartum period or knee chest position.

Heart

Edgar Allen Poe told an eerie tale of a murderer who buried the victim's corpse under the floor but was undone because his victim's heart beat with such insistent loudness that it drove the unhappy slayer to madness and final confession. Readers of James Barrie will recognize in Peter Pan the unpremeditated preview of the noises of the Hufnagel valve in the crocodile which swallowed an alarm clock and walked about ticking merrily and mysteriously from his unusual meal. Audible manifestations of the heart's activity, are an interesting though motley tribe. Perhaps it is fortunate that they are rare lest a systolic knock or an off-beat ping in our machinery be seized upon by fabricators of modern advertising mythology as resulting from a low vitamin octane rating.

Pneumoperitoneum. Even before Laennec's observation, Morgagni spoke of having heard the splash of water and air in the pericardium. Portal encountered this combination at autopsy without recording the clinical findings. Brichteau in 1844 described a Polish veteran of Napoleon's army who was struck down by a blow on the chest with a carriage tongue. His wife heard "boiling" in his chest, and Brichteau and eight assistants heard it. The man died. Autopsy disclosed pericarditis, with much evil-smelling gas. Stokes observed a lad whose trouble began with dry pericarditis but "later the sounds became so loud and singular that the patient and his wife, who occupied the same apartment, were unable to obtain a moment's repose. On examination, a series of sounds was observable which I had never before met with. It is difficult or impossible to convey in words any idea of the extraordinary phenomena then presented. They were not the rasping sounds of indurated lymph, or the leather creak of Collin, nor those proceeding from pericarditis with valvular murmur, but a mixture of the various attrition murmurs with a large crepitating and gurgling sound, while to all of these phenomena was added a distinct metallic character, and I could form no conclusion but that the pericardium contained air in addition to an effusion of serum and coaguable lymph."

James[15] surveyed the whole problem of pneumopericardium adding a case of his own. Perhaps the most remarkable example was Walshe's[16]

poor sword swallower who, during a lapse of attention, had the melancholy experience of piercing his gullet with the sword. Air was let into the pericardium and the unadvertised sound effects were heard with amazement by the audience.

Air embolism. Anyone who has heard the awful sound of air sucked in through open neck veins, churning in the heart, or seen the patient die promptly realizes why few cases are reported. Fortunately the accident is fairly rare.

Heart murmurs. Lack of interest in natural phenomena probably accounts for the fact that heart noises heard at a distance were first recorded about 150 years ago by Allan Burns.[17] Laennec observed many women with nervous palpitation whose heart throbs he heard two inches to four feet away. He postulated air in the cavities of the heart which Andral wisely discredited. Curiously Laennec, on his own death bed, had precordial noises audible several feet away. In one of Stoke's patients,[18] loud noises were "the principle cause of his suffering for his general health long continued excellent, and the heart's action was but little excited. This gentleman once observed to me that his entire body was one humming-top. The loudness of the tone varied with the force of the heart. When I first saw him the sounds were audible at a distance of at least three feet, but when the force of the heart had been reduced . . . the loudness of the sound at the aortic orifice was so much reduced as to render it inaudible, unless by applying the ear." Humming was heard over the limbs, probably transmitted by bone.

Some 30 years ago, or thereabouts, O. H. Perry Pepper used to relate the following story to his students.[19] He said that in his early days he was called in consultation to see a teen-age boy. He lived in a small street. The house was a typical Philadelphia two-story row house with four or five white marble steps leading up to the doorway. It was a warm day and the windows were open. As he stood on the doorstep waiting for the bell to be answered, he heard a rhythmical slapping or thumping sound which obviously came from the second story front bedroom. When he got upstairs to see the patient, he found a thin boy with active rheumatic heart disease, an enlarged heart, and a distended stomach containing air and fluid. The sound which he had heard on the doorstep was produced by the overactive heart percussing the stomach through the diaphragm. Dr. Pepper was kind enough to send me a reprint of his essay on "Magnified Heart sounds Due to Extracardiac Conditions with Report of an Unusual Case" published in 1912 in which a slightly reduced description of the patient is given in extensive detail.[20] It loses none of its charm from sticking more closely to facts.

Rupture of the aortic valve produces a murmur which may be heard at a distance. In his classic study, C. P. Howard,[21] one of my predecessors in the Chair of Medicine at Iowa, described 21 cases in which the murmur was heard by the patient and his friends. This number represented about a third of the nontraumatic cases. The variations in loudness of the sound are illustrated by the following reports: Quain's case, heard several

inches from the chest; O'Neill, 6 ft.; Dupuis, 15 to 20 cm.; Tranquilli, 50 cm.; Schneider, 25 cm.; and Schlecht, several centimeters. The murmur has been compared to the "croaking of a frog," "cooing of a dove or pigeon," as a "rumbling, rustling noise," a "humming noise," a "whistling noise," a "buzzing in the chest," a "musical murmur or trill," a "whining noise," and even a "rattle in the head."

Dr. Hubert Royster,[22] a distinguished surgeon of North Carolina, sent me the following story after he had read my tale of Precordial Noises. Long ago he saw in his office a negro lad, rather rheumatic in appearance. He had a heart murmur of the cooing dove type so loud that it could be heard across the small office. He had a pigeon breast deformity too. From the description of his murmur and the deformity, his family came under the happy misapprehension that he had "a pigeon in his breast." He lived for many years and died finally of congestive failure, keeping the murmur until the end.

Bellet and his associates (23) have made a notable contribution to the problem of precordial noises in their articles on musical murmurs of aortic insufficiency. They emphasized the part played by eversion of an aortic cusp diseased by syphilis. In their first paper, only one of 11 patients had murmurs heard at a distance: "The patient's bedfellow was considerably annoyed by the unusual and constant noise." In this and three other instances the murmurs were audible to the patient, presumably in the same distressing way as to Stokes' poor patient, who likened himself to a humming top. This distinction between murmurs heard by a patient but not by others suggests that vibrations may be transmitted directly to the choclear apparatus through the bone, blood vessels, or other tissues of the body rather than by air transmission. In their second series, four of 18 patients complained of hearing noises that interfered with sleep and made them nervous. One man produced such a noise that it disturbed his wife at a distance of seven feet.

While I was writing this section, an ancient squire from the Iowa farmland was brought in by a cluster of apprehensive descendants. The old man's heart squeaked whenever he took a deep breath. Nothing could be heard when I examined him unclothed. "No, no," he said, "Only when I'm dressed." Sure enough, there was a staccato cardio-respiratory squeak during deep inspiration. A little oil on his suspender pulley produced a dramatic cure. The bewildered but grateful family marched away in triumph.

Noises in the Head

When a patient complains of noises in the head, we immediately suppose that he is hearing voices but when we ourselves hear his noise we smile less wisely. In an editorial review of intracranial bruits in the *Lancet* (24) there was no mention of such noises heard at a distance from the head. However, Dr. Taylor (25) wrote me of one such patient whose noise he could hear without a stethoscope. Purves (26) and Wilcox (27) have each recorded similar findings. The explanation for these noises is that they

arise from aneurysms, arteriovenous aneurysms, or unusual distortions of intracranial vessels.

Obscure noises. Some sounds heard at a distance from the chest defy precise classification. An example of such strange cases is a footnote in Laennec's book on auscultation.[28] Andral recorded a case as follows: "I lately saw a woman who complained of palpitations of the heart. Each stroke of this organ was accompanied by a peculiar gurgling sound, which evidently came from the precordial region, andw as heard only when the heart struck the ribs; it was perceptible at a distance." Frost and Bing[29] described a healthy 22 year old woman who was seized suddenly by a "crick in the back," a sensation that something had come loose in her chest, and then pain in the chest and left shoulder. A blowing systolic murmur and some vague scratching sounds were heard along the left sternal border. Sounds came from her precordium so loud that they were heard 3 m. away. They were the synchronous with the heart beat and loudest when she was lying on her left side, disappearing when she turned to the right. Phonocardiograms showed the sounds to be systolic in time but spaced at variable intervals from beat to beat. Intensive studies failed to reveal any lesion of the lung, pleura, pericardium, or heart.

Warburg[30] described a man with mitral stenosis and auricular fibrillation observed many times in congestive heart failure. With an obscure infection he had fever and "he had heard a sound from his chest which

TABLE I
CONDITIONS CAUSING PRECORDIAL NOISES

		Total Series I and II 251 Cases	Per Cent Series II	Per Cent Series I 164 Cases
Heart murmurs		80	32	35
Pneumothorax		46	18	21
Spontaneous	30			
Traumatic	16			
Interstitial emphysema		36	14	16
Spontaneous	30			
Traumatic	6			
Pneumopericardium		27	11	15
Miscellaneous		16	6	4
Alimentary canal		13	5	5
Hufnagel valves		12	5	0
Air embolism		8	3	4
Unexplained		7	3	0
Aneurysm		4	2	0
Chest deformity		2	1	0

he described as though something were dripping; he said that he thought his heart had burst. His wife was able to hear the sound when she was lying in the bed beside him. I was able to verify his statements. At every heart beat a clicking or slightly sonorous sound was audible in the room."

Levine and Harvey[31] recorded the case of a 45-year old woman with well-compensated mitral stenosis and auricular fibrillation. After exercise, a weird sounding, rough musical murmur "was actually heard with the naked ear a foot away from the chest. . . . For several years she had been aware of a peculiar noise in her chest at times. We have heard it at irregular intervals, sometimes only for a few seconds, at other times constantly and then it might be absent for days. It is not related to position of the body or to breathing . . . There is no x-ray evidence of diaphragmatic hernia or any other abnormality that might throw light on its causation."

A Digression into Veterinary Medicine

Shortly after my original paper appeared, Dr. Eidsmoe[32] of Wisconsin told me of hearing his pony's heart thumping at a distance of 25 feet. It sounded like a drum. No explanation was available at the time but I find out from Dr. Tjalma,[33] in our Institute of Agricultural Medicine, that there are several conditions in animals which may cause sounds which can be heard at a distance from the chest. The common one is called bovine traumatic pericarditis. The unique anatomy of the digestive system in cows predisposes the reticulum, the anterior and smallest of the four divisions of the ruminant stomach, to perforation caused by swallowing foreign bodies. The reticulum lies against the diaphragm and the liver next to the diaphragm, and on the thoracic side lies the pericardial sac. The normal eating habits of cattle, abetted by rural mechanization with wire bound hay bales, nails and screws lying about, may result in short pieces of metal being swallowed. Because of the anatomical arrangements, foreign objects lodge in the reticulum. Perforation of the reticulum by such objects is favored by its honeycombed mucous surface and the powerful force of its normal contractions. Thus depending upon the size and shape of the object as well as the point of penetration, the reticulum, diaphragm and pericardium may be perforated in that sequence. The ensuing pathological processes are obvious. The resulting pneumopericarditis may be characterized by grossly audible splashing sounds. An animal in this miserable condition usually assumes a peculiar stance with the "elbows" abducted as far as possible in an effort to reduce the pain and pressure. As with the clinical counterparts, pneumopericardium, interstitial emphysema and pneumothorax in man, the sounds may not be audible at a distance but are heard readily with the stethoscope.

Comment

Beyond serving as a repository for esoterica, is there usefulness in collecting such diverse disorders with the common denominator of noise

heard at a distance from the chest? Certain gleanings reward closer study. Loud heart murmurs are the commonest cause of the phenomenon, followed by interstitial emphysema, pneumothorax, and pneumopericardium. Records of the other conditions are less numerous. From the topographical and mechanical view, air free in the chest from the interstitial emphysema or pneumothorax, spontaneous or accidental, heads the list; cardiac murmurs come next and then pneumopericardium. Since the sources of this review have been casual and the survey sporadic, the data are not representative. In some specialties, particular problems may be missing or too heavily represented. A surgeon's reading and experience would no doubt assemble a different array.

The general problem may be considered in interstitial emphysema of the lung. In such a disturbance noises heard at a distance are an exaggeration of a sign much oftener confined to the chest and heard only with the stethoscope. Noises heard at a distance may be so loud as to command instant notice or may be heard by the unaided ear only after being heard with the stethoscope and then listened for attentively. Phonocardiographic records, of which several are reported, serve to demonstrate the sometimes irregular timing of such noises during systole and perhaps quiet the suspicion of skeptics that they are illusions. What constitutes the urge to publish case reports has never been known, but one has only to hear these eerie sounds to appreciate the high clinical drama. Published cases represent an unknown fraction of those met clinically. Illuminating papers, such as Louis Hamman produced, were followed by a wave of case reports, and a useful diagnostic sign caught popular fancy and became a medical fashion.

Clinical features of spontaneous interstitial emphysema of the lung may suggest acute myocardial infarction, but usually the complaint of pain in the chest is more insistent than the meager signs of difficulty. The patient is in pain but looks well, usually breathes easily, and is not in shock. Generally he is young, vigorous, and active, without signs or a history of hypertension, angina, or vascular disease. Later reactions, such as fever, leukocytosis, and rapid erythrocyte sedimentation, do not follow. Such a loud noise may be produced only in certain positions, so that change of position or movement will enhance or quiet the ticking chest. The noises have been audible at a distance in about 10 per cent of the recorded cases. The loudest noise, measured in distance heard, was perceived 20 feet from the patient. Duration varied from two hours to two weeks. There was much variation in the intensity; sometimes everything would be quiet and then the sounds would return. As a general rule, they would come and go. In all except one case, the sounds were heard best with the patient lying on the left side, and many could demonstrate the sound at will by assuming the proper position. I saw one young man whose main distress was not the pain in the chest but the fact that the noise coming from his chest was so loud his wife made him sleep in the next room. He could not turn and eliminate it, but finally it went away, and he gained his reprieve. Several other reports

suggest that such noises are a rare cause of temporary domestic infelicity. They alarm patient and family. Indeed, fear and curiosity occasionally have brought the patient to the doctor, since there may be little pain.

Subcutaneous emphysema has been recorded in only a few cases, but since it may be confined to a small area and be ephemeral it is easily overlooked. In almost all cases of interstitial emphysema of the lung, if complicating pneumothorax occurred it was on the left side. Often it has been so small that only careful search with proper alignment has produced diagnostic roentgenographic shadows. Right-sided pneumothorax does not appear to be rarer than left-sided, but only rarely has it been found in association with the crunching, bubbling, paper-rustling sound (Hamman's sign) so characteristic of mediastinal emphysema. The most comprehensive discussion of such sounds in interstitial emphysema was given by Greene, who differentiated between two classes of sounds. "The bubbling, crunching, clicking and some of the tapping sounds are due to the heart rubbing against emphysematous blebs in interstitial emphysema of the lung and mediastinum. The knocking and tapping metallic sounds, on the other hand, are due to the heart striking an emphysematous bleb on the median aspect of a partly collapsed left lung or the diaphragm immediately over a gas bubble in the splenic flexure of the colon in the presence of pneumothorax on the left side." The evidence on which these conclusions are based is the fruit of carful study, and, short of detailed human experiments, is the best we are likely to get from observing the effects of accidents and disease.

Diagnosis of such rare conditions is important, since the cause may be a mechanical crisis that can be corrected or eased. Delay or confusion may be fatal. On the other hand, if the casual condition is innocuous, it is well to avoid mistaking it for conditions of ominous import. In order of urgency, the Mühlengeraüsch or mill wheel sound of air embolism stands first. Its clinical debut, always unexpected, is associated with an opening by wound, scalpel, or needle by which air gets into veins. Immediate rotation to the left lateral position or the Trendelenburg position, trapping air bubbles above the blood in the right ventricle where they may be aspirated with a needle and syringe, may be lifesaving. Inhalation of 100 per cent oxygen may help.

Rupture of the esophagus, which I have seen produce Hamman's sign, probably can cause loud noises, even without pneumopericardium. Since surgical cure in such a calamity may now be anticipated, the diagnosis of a ruptured gullet should be considered, especially in cases in which a history of extreme vomiting or instrumentation makes the condition probable.

Traumatic pneumothorax, pneumopericardium, and pneumomediastinum with the connotation of crushed ribs or penetration by a missile or foreign body, obviously require urgent treatment. The attending noise may indicate the extent of damage, which otherwise is not apparent. Treatment is that of the underlying condition.

Spontaneous interstitial emphysema of the lung implies pneumothorax

and, at times, the hazard of tuberculosis. The noise heard at a distance has not been nearly so ominous as it has seemed to the victim, always amazed and often terrified by such uncanny behavior. Thus, diagnosis usually permits reassurance, since in all recorded cases the patients have survived. It should be kept in mind that tension pneumothorax may lurk under this clinical camouflage. Also, "air lock," the dissection of air through the lung or hilum under pressure to impede blood flow, may require administration of 100 per cent oxygen or surgical intervention to stop the leak. In general, the major role of the physician is to calm terror by bringing assurance.

Noise from the alimentary canal may rarely lead to the discovery of hiatus hernia with an errant stomach or colon. Loud murmurs, when they have arisen out of the innocuous quiet of the past, especially under some stress or accident, may call to mind the likelihood of ruptured aortic valve or the turning inside out of a syphilitic valve cusp. Giving a better view of prognosis, such diagnostic tours de force escape the odium of academic banality.

SUMMARY

A variety of clinical conditions that may be associated with precordial sounds heard by the unaided ear at a distance from the chest is assembled, compared, and assessed. The commonest causes of such sounds are cardiac murmurs produced by valve rupture or other lesions, often abrupt in onset and a consequence of stress or strain. Next in order of frequency come interstitial mediastinal and pulmonary emphysema, both spontaneous and traumatic. These are followed by spontaneous and traumatic pneumothorax, pneumopericardium, noises the heart produces by striking air-containing gut, air embolus, and a small mysterious miscellany of unexplained sounds. Since the noises have diverse sources there is no pathophysiological common denomiator to compare with the clinical fact of abnormally great volume of sound. With such differences in cause and, hence, in necessary treatment and prognosis, attention should be directed to the cause, which usually comes to light on careful clinical scrutiny.

Four additional years of searching have added some new pearls to my strand, but it is far from complete. I introduced the heresy that children do not have such sounds because they had small hearts and small thoracic sounding boards. Looking for such noises, Dr. John Wild and I found them nine times in children, even infants, with such lesions as ventricular septal defects, aortic or pulmonic stenosis or tricuspid atresia. Hufnagel valves, being more prevalent, have added to the list. Aortic aneurysms, going all the way back to Lancisi, have added four; and chest deformity, myxoma of the left auricle, ruptured tendinous cords, pneumoperitoneum and a murmuring spleen have swelled the list. Our knowledge of the mysterious complexities of clinical medicine grows with experience perceived, understanding disciplined and inquiry directed. We find what is there only if we sacrifice that part of ourselves which is given in complete attention and concentration. We see and hear what is

there only if we look, listen, and focus. We find what we search for not what we look at.

If the spirit of Robert Hooke were with us tonight, his interest in natural phenomena would have had some stimulus, and perhaps he would be amused at my answers to his query, "Who knows but that one may discover the works performed in the several offices and shops of a man's body by the sounds they make, and thereby discover what instrument or engine is out of order!" This commemorative tribute I trust Louis Mark would have enjoyed and given his approval. Finally, lest too much astringent mirth make you think the subject is not important, I conclude, in all humility, with a verse of scripture (Jeremiah 17:9): "The heart is deceitful above all things. . . . Who can know it "

Acknowledgments: Collecting the material for this paper has been a very happy experience because though some of the noises described are tragic, many are not, and amusing and embarrassing situations may occur. I have been particularly grateful to a large number of friends and strangers who have told me or written me about some specially fabulous case of their own or their personal experience with pneumothorax and interstitial emphysema. Many, but not all, have been mentioned in the references. I am grateful to Miss Nina A. Frohwein for assistance with references. I am particularly grateful to my secretaries, Mrs. Charlotte Fell and Miss Eula Van Meter, for their patience with me and the numerous drafts of the paper, corrections, proofreading, for without them I would be lost.

RESUMEN

Hay una variedad de afecciones que pueden asociarse a ruidos precordiales que se pueden escuchar con el oído a cierta distancia del pecho. Estas afecciones se reumen, se comparan y se valúan. Las causas más comunes son los soplos cardiacos producidos por ruptura valvular o por otra lesión a menudo de principio repentino y como consecuencia de esfuerzo o de "stress." Enseguida vienen por su frecuencia el enfisema mediastinal intersticial y enfisema pulmonar tanto espontáneos como traumáticos.

Estos son seguidos por neumotorax espontaneo o traomatico, neumopericardio, o los ruidos que el corazón produce al golpear intestino conteniendo aire, embolias gaseosas y pequeños ruidos misteriosos no explicables. Puesto que los ruidos tienen origines diversos no hay un denominador común fisiopatológico para comparar con el hecho clínico de los sonidos anormales de gran volumen. Con tales diferencias causales debe procurarse investigar ésta para realizar el tratamiento necesario. La causa puede aparecer generalmente después de cuidadosa investigación.

Por cuatro años más de investigación he agregado nuevas perlas a mi colección, pero está muy lejos de ser completa. Introduje la herejía de que los niños no tienen tales ruidos porque tienen corazones pequeños y pequeñas cajas de resonancia torácica. Buscando tales ruidos el Dr. John Wild y yo encontramos nueve en niños aún en infantes con tales lesiones como defectos septales ventriculares, estenosis aórtica y pulmonar o atresia tricuspídea. Las válvulas de Hufnagel siendo ahora más comunes, se han agregado a la lista. Los aneurismas aórticos retrocediendo hasta Lancisi han agregado cuatro; y la deformación torácica, el mixoma de la

aurícula izquierda, ruptura de las cuerdas tendinosas, neumoperitoneo y el soplo esplénico han hinchado la lista. Nuestro conocimiento de las misteriosas complejidades de la medicina clínica, crece con la experiencia, con la disciplina e investigación dirigida. Encontramos que así sucede si hacemos el sacrificio de nosotros concentrándonos en la tención. Vemos y oimos si buscamos, escuchamos y enfocamos. Encontramos lo que se busca no sólo lo que miramos. Si el espíritu de Roberto Hooke estuviera con nosotros esta noche su interés en los fenómenos naturales sería de estímulo y probablemente le divertirian mis contestaciones a su pregunta "Quién sabe lo que uno podría descubrir?"

ZUSAMMENFASSUNG

Eine Vielzahl von klinischen Bedingungen wird zusammengestellt, verglichen und beurteilt, die verbunden sein können mit präcardialen Geräuschen, wie sie für das unbewaffnete Ohr entfernt von der Brustwand hörbar sind. Die häufigste Ursache für solche Töne sind Herzgeräusche, die durch Klappenruptur entstehen oder durch andere Veränderungen, oft abrupt im Beginn und als Folge einer Belastung oder einer Überanstrengung. Am nächsten in der Reihenfolge der Häufigkeit kommt das interstitielle mediastinale und pulmonale Emphysem, sowohl das spontane wie das traumatische. Darauf folgt im Rang der spontane und traumatische Pneumothorax, das Pneumopericard, Herzgeräusche entstanden durch anschlagenden lufthaltigen Darm; weiter folgt die Luftembolie und ein kleines rätselvolles Gemisch von nicht erklärbaren Geräuschen. Weil die Töne verschiedene Quellen haben, gibt es keinen gemeinsamen pathophysio-logischen Nenner zum Vergleich des klinischen Tatbestandes eines abnorm grossen Geräusch-Volumens. Mit solchen Unterschieden in der Entstehung und deshalb auch der notwendigen Behandlung und Prognose muss sich die Aufmerksamkeit auf die Ursache richten, die gewöhnlich ans Licht kommt bei sorgfältiger klinischer Überprüfung.

4 weitere Jahre der Forschung haben mich zwar einige neue Erkenntnisse gewinnen lassen, aber es fehlt noch viel, um vollständig zu werden. Ich brachte die Irrlehre auf, wonach Kinder keine solchen Geräusche aufweisen, weil sie kleine Herzen haben und kleine thorakale Resonanzböden. Auf der Suche nach solchen Geräuschen fanden Dr. John Wild und ich sie 9-mal bei Kindern, sogar Kleinkindern, mit Befunden wie Ventrikel-Septum-Defekt, Aorten- und Pulmonal-Stenose oder Trikuspidal-Atresie. Hufnagel-Klappen, die häufiger sind, wurden der Liste hinzugefügt. Aorten-Aneurysmen, die bis zu Lancisi zurückgehen, kamen hinzu; Thoraxverformung, Myxom des linken Herzohres, Rupturierte Sehnenfäden, Pneumoperitoneum und eine tönende Milz haben die Liste anschwellen lassen. Unsere Kenntnis der rätselhaften Verflochtenheiten der klinischen Medizin wächst mit wahrgenommener Erfahrung, geschultem Verständnis und unmittelbarer Untersuchung. Wir finden nur dann heraus, was vorliegt, wenn wir jenen Teil von uns selbst aufopfern, der zu gänzlicher Aufmerksamkeit und Konzentration führt. Wir sehen und hören, was vorliegt nur, wenn wir schauen, lauschen und die Richtung genau bestimmen. Wir

entdecken, wonach wir forschen, nicht, wonach wir schauen.

Wär der Geist Robert Hooke's heute abend unter uns, würde sein Interesse an den Phänomenen der Natur einigen Ansporn gegeben haben, und vielleicht hätte er Freude behabt an meiner Antwort auf seine Frage, "Wer es erlebt, dass man die Vorgänge, die in den verschiedenen Büros und Geschäften des menschlichen Körpers geschehen, an den Geräuschen erkennen kann, die sie verursachen und dadurch feststellt, welches Instrument oder Gerät in Unordnung ist." An dieser Gedächtnisehrung würde Louis Mark, wie ich hoffe, Vergnügen gehabt und ihr zugestimmt haben. Damit am Ende endlich nicht zuviel hemmende Heiterkeit. Sie zu dem Gedanken veranlasse, dass der Gegenstand nicht von Wichtigkeit sei, schliesse ich in aller Demut mit einem Vers aus der Heiligen Schrift (Jeremia) 17,9) : "Arglistig ist das Herz mehr als alles andere . . . wer kann es ergründen?"

REFERENCES

1 Bean, W. B.: "Precordial Noises Heard at a Distance from the Chest," *J.A.M.A.*, 152:1293, 1953.

2 Asher, P.: Personal letter.

3 Bricheteau: "Observation d'hydro-pneumo-péricarde, accompagnée d'un bruit de fluctuation perceptible à l'orielle," *Arch. Gén. Méd.* 4th series, 4:334, 1844.

4 Rees, W. A. and Hughes, G. S.: "Wounds of the Chest as seen at an Advanced Operating Centre," *Lancet*, 1:55, 1918.

5 Munden, W. P. H.: "Memoranda," *Brit. Med. J.*, 1:174, 1918.

6 Scadding, J. G. and Wood, P.: "Systolic Clicks Due to Left-Sided Pneumothorax," *Lancet*, 2:1208, 1939.

7 Hamman, L.: "Spontaneous Interstitial Emphysema of the Lungs," *Trans. Assoc. Am. Physicians*, 52:311, 1937. (The classic paper.)

8 Pinckney, M. M.: "Mediastinal Emphysema and Idiopathic Spontaneous Pneumothorax," *Va. Med. Mo.*, 68:315, 1941.

9 Curtin, R. G.: "Cardio-esophageal Gush and Click," *Med. News*, 75:330, 1889.

10 January, L.: Personal communication.

11 Greene, J. A.: "Unusual Sounds Emanating from the Chest," *Arch. Int. Med.*, 71: 410, 1943.

12 Allan, F. N.: "Heart Noises," *New England J. Med.*, 218:655, 1938.

13 Cottrell, J. E.: "Personal Communication and Reference to Translation of Nicolas Tulp's Observation." This Also Appears in an Article by Sailer, J.: "Pulsating Spleen in Aortic Insufficiency," *Am. Heart J.*, 3:447, 1928.

14 Fisher, W.: Letter and case abstract.

15 James, W. B.: "Pneumopericardium," *Trans. Assoc. Am. Physicians*, 19:351, 1904.

16 Walshe quoted by James.

17 Burns, A.: *Observations on Some of the Most Frequent and Important Diseases of the Heart.* Pp. 187-189. Thomas Bryce, Edinburgh, 1809.

18 Stokes, W.: *Diseases of the Heart and the Aorta.* Lindsay & Blakiston, Philadelphia, pp. 37, 1855.

19 Cottrell, J. E.: Personal communication.

20 Pepper, O. H. P.: "Magnified Heart Sounds Due to Extracardiac Conditions with Report of an Unusual Case," *J.A.M.A.*, 58:340, 1912.

21 Howard, C. P.: "Aortic Insufficiency Due to Rupture by Strain of a Normal Aortic Valve," *Canad. Med. J.*, 19:12, 1928. Comprehensive and detailed study with many gleanings from forgotten and out of the way reports. Source for most subsequent reviews.

22 Royster, H. A.: Personal letter.

23 Bellet, S., Gouley, B., Nichols, C. F. and McMillan, T. M.: "Loud Musical Diastolic Murmurs of Aortic Insufficiency," *Am. Heart J.*, 18:483, 1939.

24 Editorial: "Intracranial Bruits," *Lancet*, 1:239, 1956.

25 Taylor, F. R.: Personal letter.

26 Purves, G. H.: "Whistling Noise Over the Temporal Area," *J.A.M.A.*, 152:774, 1953.

27 Wilcox, M. B.: "A Bruit in the Left Ear," *J.A.M.A.*, 153:1231, 1953.

28 Laennec, R. T. H.: De l'auscultation médiate; Brosson et Chaudé, Paris, 1819. Forbes Translation of Ed. 3, Samuel and William Wood, N. Y., 1838.

29 Frost, J. and Bing, J.: "Some Cases of Precordial Sounds Audible at a Distance," *Acta Med. Scand.*, 105:411, 1940.

30 Warburg, E.: "Cardiac Murmurs Audible At-a-Distance—Mitral Stenosis Thrombosis in the Right Ventricle, Pulmonary Infarction," *Acta Med. Scand.*, 107:503, 1941.

31 Levine, S. A. and Harvey, W. P.: *Clinical Auscultation of the Heart*, W. B. Saunders Co., Philadelphia & London, 1949.

32 Eidsmoe, N. A.: Personal communication.

33 Tjalma, R. A.: Personal communication.

34 Wild, J. and Bean, W. B.: Unpublished observations.

35 Dock, W.: *Heart Sounds, Cardiac Pulsation, Coronary Artery Disease.* The Porter Lecture. U. of Kansas Press, 1956.

36 Calo, A.: I soffi extra-cardiaci diastolici A proposito di un soffio cardio-polmonare musicale udibile a distanza. Reggio Emilia Poligrafica Reggiana, 1952.

37 Palfrey, F. W.: "A Case of Chronic Infective Endocarditis with Ulceration of Chordae Tendineae," *Boston Med. and Surg. J.*, 167:55, 1912.

38 Love, J. K.: "Case of Hydro-Pneumopericarditis," *Lancet*, 1:319, 1888.

39 Bubis, J. L.: "Acute Pericarditis Following the Removal of Gonorrheal Pyosalpinx," *Clieveland Med. J.*, December, 1908.

40 Young, R. D. and Hunter, W. C.: "Primary Myxoma of the Left Ventricle with Embolic Occlusion of the Abdominal Aorta and Renal Arteries," *Arch. Path.*, 43: 86, 1947.

41 Duboczky, B. O.: "Loud Millwheel Murmur Presumably Caused by Air Embolism In a Patient with Pneumoperitoneum," *Am. Rev. Tuberc.*, 70:1092, 1954.

42 Bourne, G.: "Clicking Pneumothorax Simulating Myocardial Infarction," *Lancet*, 1:1122, 1957.

Developments in the Therapy of Hypertension

An increasing number of reports over the past two years, indicate that blood pressure elevation which is adequately severe and which exists for a prolonged period of time, will produce progressive vascular in the brain, the heart, and the kidneys. The more severe the hypertension, the more marked these changes will be. Observations made on renal function in hypertensive patients indicate that effective reduction in the blood pressure may completely arrest these vascular changes in the kidneys regardless of the method used for blood pressure reduction. Although the vascular changes are arrested, function rarely returns to normal.

Hypertension aggravates and hastens the development of arteriosclerosis. Reducing the blood pressure arrests this hastening process, but still arteriosclerosis progresses just as it does in the normotensive individual. The method of blood pressure reduction here too is probably not important. Sympathectomy is effective in reducing the blood pressure when concurrent medical therapy is used in those patients who do not respond to sympathectomy alone. There is no serious objection to this approach just as long as the blood pressure is severe enough to warrant surgical therapy and the surgeon is proficient at doing sympathectomies. On the other hand, when the psychiatrist, or the generalist, or the internist who carries psychiatric overtones, can talk the blood pressure down, this is good therapy. Unfortunately this is rarely possible in the patient who has a diastolic hypertension which is fixed, especially when the diastolic pressure is fixed above 120 mm. Hg.

Any drug therapy that is effective in bringing the blood pressure to a normal or relatively normal level, is an effective therapeutic program. Generally speaking, the most effective therapeutic program has been one of polypharmacy, in which an attempt is made to deplete body sodium with Chlorothiazide (Diuril). Then, drugs are given which depress the sympathetic nervous system. The centrally acting drugs are used first. The most common ones are Rauwolfia and hydralazine (Apresoline). Usually in milder cases Rauwolfia is recommended and if the patient needs additional therapy, hydralazine may be added. In the more severe cases, a therapeutic trial of hydralazine with rauwolfia may be employed, but when the diastolic blood pressure is fixed above 120 to 130 mm. Hg., ganglionic blocking agents must usually be given for adequate control.

An effective program of drug therapy is to start the patient on 500 to 1,000 mg. of chlorothiazide twice a day. After one week, Rauwolfia (Alseroxylon) is given in addition to the chlorothiazide starting with a dose of 8 mg. (4 tablets) a day. After two weeks the dose of Alseroxylon

TABLE I

THERAPEUTIC APPROACH TO THE PATIENT WITH HYPERTENSION

Severity of Hypertension	Initial Therapy	Adjunctive Therapy*
Systolic blood pressure elevation diastolic blood pressure <100 mg. Hg.	None	None
Diastolic blood pressure >100 mm. Hg. but <120 mm. Hg.	Chlorothiazide	Rauwolfia or Rauwolfia + hydralazine
Diastolic blood pressure >120 mm. Hg.	Chlorothiazide + Rauwolfia	Hydralazine or ganglion blocking agent
Severe progressive hypertension	Chlorothiazide + Rauwolfia	Ganglion blocking agent†

*Adjunctive therapeutic agent to be added to regimen if initial therapeutic agent is found to be inadequate alone.

†Must be added without delay when indicated.

is reduced to 4 mg. per day. This regimen is then continued for approximately one month in mild to moderately severe disease to test for maximum responsiveness. When the response is not adequate hydralazine can be added, starting with a dose of 25 mg. after each meal and at bedtime but the doses should be given at least four hours apart. The does is increased in 25 mg. increments until a maximum of 600 mg. per day is given. When the patient is not responsive to this drug, it should be discontinued in preference for a more effective drug. Because of the potential side effects, hydralazine should not be continued when it fails to produce the desired therapeutic results.

Patients with severe disease, particularly those with papilledema will usually require the administration of a ganglionic blocking agent in addition to the Chlorothiazide and rauwolfia. There are some points of importance to note when the use of ganglionic blocking agents is anticipated. The first problem is effective dose titration. It is highly important to start with a small dose of the ganglionic blocking agent, gradually increasing the dose until the standing pressure reaches the desired level, usually about 150/100. The therapist should use not only blood pressure observations in the office, but also use symptomatology to arrive at the proper dose. If the patient comes in and says he has attacks of dizziness at certain times during the day, this is adequate to show that he is getting excessive hypotension at that time. Using symptoms plus the blood pressure observations (using home blood pressures in some patients) regulation of blood pressure is less difficult. When Pentolinium (Ansolysen) is used, the initial dose of the blocking agent is 20 mgm. taken after breakfast and supper. The dose is increased in 20 mgm. increments at weekly intervals until the standing blood pressure reaches the desirable levels. When Mecamylamine (Inversine) is used it is started at a dose of 2½ mg. at breakfast and supper, followed by giving a daily lunch dose of 2½ mg.

After one week the lunch dose is gradually increased, then the breakfast dose is increased and so on. The supper dose trails behind. Because the drug action lasts a long period of time, the patient should receive the biggest doses in the morning, and at lunch since at night when he is relaxed, he does not need nearly as much drug. If a large dose is taken at night, when the patient gets up in the morning after a period of relaxation, he may experience excessive hypotension.

In using ganglionic blocking agents, it is usually a good idea to use them in combination with Rauwolfia, because the combination not only blocks the sympathetic nervous system, in the brain, and at the ganglia simultaneously but in addition the sedation and tranquility from the Rauwolfia compound is obtained.

The problem of constipation: This is an ever present problem associated with the use of ganglionic blocking agents because not only are the sympathetic ganglia blocked with these compounds but also the parasympathetic ganglia are blocked which results in constipation. The therapist must be very vigilant against constipation, and use cathartics freely. The cathartic of choice is a matter of trial and error. Cascara is probably the best. There are a number of compounds available in tablet form, such as Dorbane. The elixir of Cascara Sagrada is likewise very effective. Some patients do not do so well with cathartics, and will do much better with Prostigmine in a dose of 15 to 30 mg. about an hour before breakfast. On the other hand, some patients get rather severe cramps with Prostigmine and do better with the cathartics. The therapist must find by trial and error which is the best for the individual patient. At the beginning of the treatment, it is difficult to arrive at the precise method of therapy for any one particular patient.

Renal Damage: When renal function is depressed due to advanced damage to his kidneys, the kidneys are not able to adjust when the blood pressure is reduced too rapidly or excessively because of the vascular spasticity. If the kidneys are already functioning poorly because of the vascular damage, bringing the blood pressure down may actually temporarily enchance existing renal failure. However, when the blood pressure is controlled for a prolonged period of time, progressive vascular changes are arrested. Therefore, in the patient who has an elevation in the BUN, the therapist should probably not reduce the blood pressure to the normotensive level immediately. After a month of blood pressure regulation, he can usually adjust it without functional depression. When the BUN is normal before treatment, the blood pressure can be reduced to normotensive ranges without worry. If the blood urea nitrogen is 30 to 60 mg. per cent usually the blood pressure in the standing position should not be reduced below 170 systolic and 110 diastolic. When the BUN is 60 to 100 mg. per cent, the blood pressure should not be reduced much below 190/120 initially. Then after the pressure is regulated at this level for two to four weeks, it can gradually be brought to normotensive levels without further aggravating the renal failure. When the BUN is more than 100, it is hopeless unless they have concomittant heart failure. The mortality in our patients, when

the blood urea nitrogen was more than 100 mg. per cent was 100 per cent, and we have not helped the patient by reducing the blood pressure; this again indicates that it is best to treat the patient before the vascular damage has progressed beyond the point of no return.

Finally unless the therapist finds means and methods for stabilizing his patient as far as his reactions to his environment are concerned, he is going to have a pretty difficult problem regulating doses of the drugs, because the drug is used at a fixed dose, which is not nearly as effective as the hemostatic body mechanism would be under normal conditions. So again, there are definite limitations to the drug therapy of hypertension.

JOHN H. MOYER, M.D.*
Philadelphia, Pennsylvania

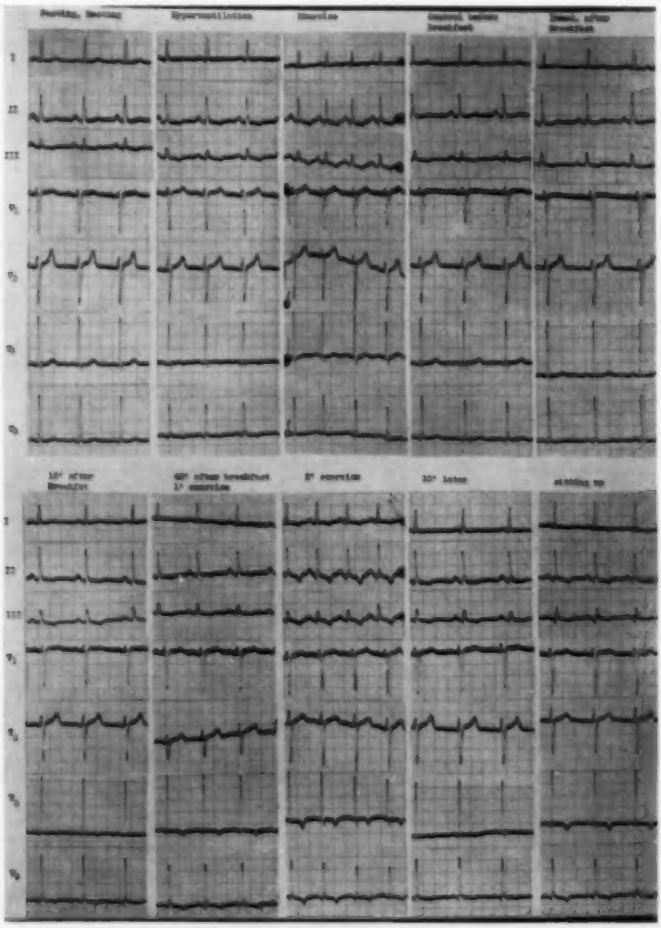
*Professor of Medicine, Department of Internal Medicine, Hahnemann Medical College and Hospital.

THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

During the examination of a 33 year old man who had applied for a position as an airplane pilot an electrocardiogram was encountered that showed small inverted T waves in the left precordial leads. There was no history and no other signs that suggested heart disease. In an attempt to investigate the electrocardiogram more fully records were made as shown in figure 1.

It is to be noted that the electrocardiogram made under basal conditions is entirely within normal limits. When hyperventilation and exercise are performed by the fasting patient the T waves in Leads II, V5 and V6 became inverted but returned to their basal form within a short period of time (see "control before



breakfast"). Not immediately following a meal, but fifteen minutes later there are T wave changes in Leads II, V5 and V6 that remain constant for more than forty minutes. Hyperventilation and exercise produce more marked effects now than they did while fasting. Additionally, three minutes of vigorous bicycle exercise results in inversion of the T wave in Lead I. Ten minutes later this effect is gone, the tracing having largely returned to the form that resulted from food alone. Both in the limb leads and precordial leads the T waves could be inverted by having the patient sit up.

There was no history suggesting a cardiac lesion and the physical examination and X-ray studies revealed no evidence of heart disease of any kind.

The electrocardiographic study shows, in general, T wave changes that we found to be common among young healthy adults 18-28 years of age: Lowering and inversion of T waves in Leads with large R waves result from increasing rate, exercise, and other non-pathologic conditions that diminish the magnitude of the ventricular gradient. The inversion of the T wave in Lead I that occurs in this case will attract much attention. There is sound basis for concluding that the T wave may occasionally be inverted in Lead I in the absence of disease especially in the circumstances under which it is encountered here. However, the incidence of this finding among normals under ordinary circumstances is so small that it is bound to be held suspect under any circumstances.

We believe that the inversion of the T waves in this case, occurring under the circumstances indicated, are probably not produced by disease. We base our conclusion upon the confidence that we have in the physiologic approach to electrocardiographic interpretation. In order to record an opinion that an inverted T wave in Lead I may be normal we recognize that it is necessary to overcome a rather deep-rooted prejudice that grows in the soil of the statistical approach to the limitations of normal variations. Since the statistical approach has been so confusing in relation to so many electrocardiographic problems it is perhaps time to uproot some of the prejudices that have grown out of it.

Unfortunately, as so often occurs, we can not be absolutely certain that our conclusion in this case is correct, for an antero-lateral zone of epicardial ischemia can also diminish the magnitude of the ventricular gradient and thus cause similar inversion of the T waves. However, when ischemia is responsible for small inverted T waves, exercise will generally cause the T waves to become upright again. On the other hand, if the diseased area of myocardium is represented by scar tissue, with little or no surrounding ischemic zone, the electrocardiogram may well behave as it has in this case. In the latter case QRS changes that reveal the presence of such scarring may not be discernible.

MANUEL GARDBERG, M.D. and IRVING L. ROSEN, M.D.*
New Orleans, Louisiana

*From the Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School.

Case Report Section

Cardiac Dysfunction in Severe Hyperkalemia*

LAWRENCE H. GOLDEN, M.D., F.C.C.P.**
New Orleans, Louisiana

The clinical manifestations of hyperpotassemia are well described in the current literature, and the electrocardiogram is one of the most important diagnostic aids in establishing this syndrome. This paper is primarily concerned with the management of the often dramatic electrocardiographic abnormalities seen in patients with hyperkalemia.

The electrocardiograph was first used to demonstrate the effects of abnormal serum levels of potassium in the animal laboratory in 1938 by Winkler [1] and again by Chamberlain [2] in 1939. Since that time many investigators [3-7] have described similar alterations in the electrocardiograms of human beings with hyperpotassemia.

The progressive electrocardiographic changes seen with rising serum potassium have been summarized by Burch and Windsor [8] as follows:

1. Increased magnitude of T waves.
2. Depression of the ST segment.
3. Disappearance of U waves.
4. Increased duration of the QRS complex.
5. Increased PR interval.
6. Distortion of P wave with a decrease in magnitude.
7. Prolongation of QRS to produce a pattern of bundle branch block.
8. Auricular standstill.
9. Ventricular fibrillation.

The most characteristic change seen in peaking of T waves and increase in the duration of the QRS complex.

Attempts at correlation between serum levels of potassium and electrocardiographic alteration are difficult, since it is the intracellular potassium which is important in determining the cardiac muscle response. Tarail [9] pointed out that with serum levels of 6.8-7.6 mEq/liter, the electrocardiogram showed inconstant changes, but when the serum level was over 7.8 mEq/liter, the changes were consistently present.

The following case of acute glomerulonephritis demonstrates many of the typical abnormal electrocardiographic features of hyperkalemia.

The patient was an 18 year old airman who had streptococcal pharyngitis in October, 1955 which was treated with penicillin. Early in November, 1955, he had recurrent sore throat but did not seek medical attention. In December he was hospitalized with complaints of pain and swelling of both knees and wrists and a rash on the lower legs. Past history was negative.

*From the 3650th Air Force Hospital, Sampson A.F.B. Geneva, New York.
**Tulane University School of Medicine, Department of Medicine, New Orleans, Louisiana.

Physical examination revealed an acutely ill, well developed, well nourished man. Blood pressure was 115/70, temperature 99.8° F., pulse 92, respirations 20. The examination of the head, including eyes, ears, nose, and throat, was negative except for slight infection of the pharynx. His neck was supple and his chest and lungs normal. The heart rhythm was regular and a grade I systolic murmur was heard at the apex. There was no palpable thrill or friction rub heard. The pulmonic second sound was slightly accentuated. The abdomen, back and genitalia were normal. The joints and extremities exhibited slight swelling of ankles but no erythema or increase in temperature was noted. Extensive purpuric lesions were present over both lower extremities.

On admission the white blood cell count was 15,000 with 82 polymorphonuclear leukocytes, hematocrit 45 per cent, sedimentation rate 36 mm. per hour. The urine was negative for sugar, albumin, and microscopic findings. A chest x-ray film and electrocardiogram were normal. A throat culture was negative for Beta hemolytic streptococcus. Platelet count, bleeding and clotting time, clot retraction, prothrombin time, and capillary fragility tests were all normal.

In the first month, the illness was that of the rheumatic state. The laboratory and electrocardiographic studies gave confirmation of active myocarditis. During this

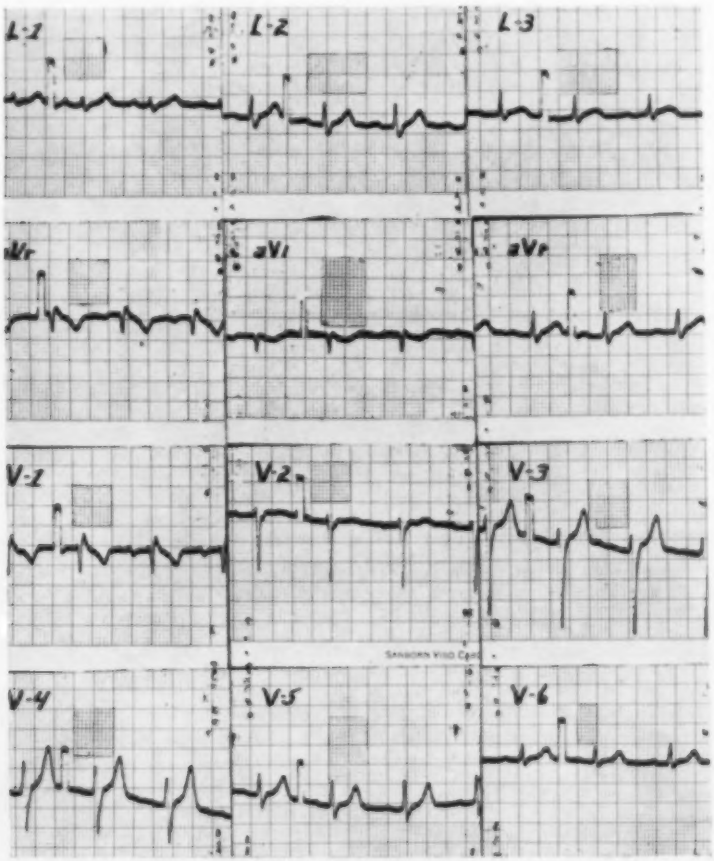


FIGURE 1: Base line electrocardiogram. Low voltage is present in Lead I. The auricular and ventricular conduction times are normal. The voltage and form of the T waves were considered to be within normal limits.

time abdominal pain was a frequent complaint. Radiographic studies of the gastrointestinal tract were not helpful. The arthritis and purpura gradually cleared but fever persisted.

In the fifth week of hospitalization the urine exhibited microscopic red blood cells, albumin and casts. During the course of the next week, he developed pleural effusion, weight gain of 20 pounds, peripheral edema, and elevation of blood pressure to 160/100. The laboratory findings demonstrated early uremia and mild acidosis. A urine culture showed the presence of Escherichia coli, and he was treated effectively for this with chloromycetin.

The disease progressed, and with the urine output gradually dropping, he became more uremic and acidotic. The urea nitrogen was 60 mg. per cent, hematocrit 30 per cent, CO_2 combining power 41 vol. per cent. A supportive regimen including restricted salt intake, digitalization, and small blood transfusions was carried out, without improvement.

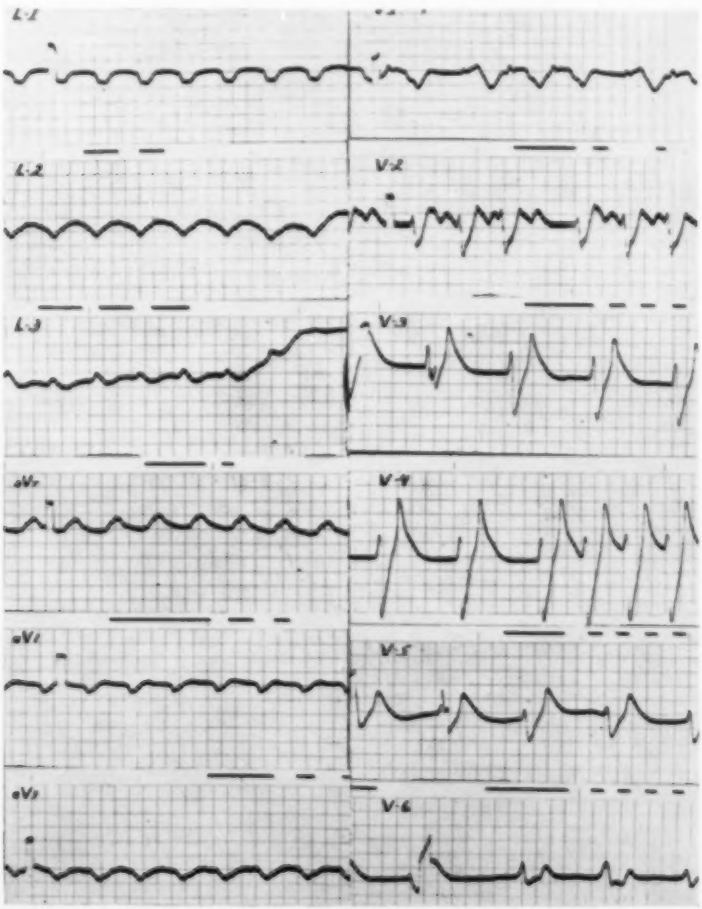


FIGURE 2: Serum potassium recorded 8.6 mEq./liter at this time. Electrocardiogram exhibiting peaked T waves, diminution of the R wave. A-V dissociation with widening of the QRS, depression of ST segment and merging of the QRS and T waves into a sine wave.

At the end of the eighth week of hospitalization, the serum potassium rose to 7.0 mEq./liter. The use of retention enemas with potassium-removing resins effected temporary reduction to 6.4 mg. On February 13 and again on February 22, he was dialyzed by Dr. Arthur MacNeill and staff of the University of Buffalo, using the MacNeill Mark XI-b dialyzer.[15] The second dialysis produced a good chemical response with the blood urea nitrogen dropping from 170 mg. per cent to 90 mg. per cent. Subjectively he was improved, though renal function remained severely impaired.

On March 3, he developed acute hyperkalemia with serum potassium of 8.6 mEq./liter. Clinically this was manifested by Cheyne-Stokes respirations, marked lethargy and dramatic alteration of the electrocardiogram. Figure 1 shows the electrocardiogram taken on December 29, 1955. At this time regular sinus rhythm was present with normal auricular and ventricular conduction times. The T waves are not considered grossly abnormal and electrolyte imbalance is as yet not evident from our laboratory procedures. Figure 2 shows the electrocardiogram at the time of the increase in serum

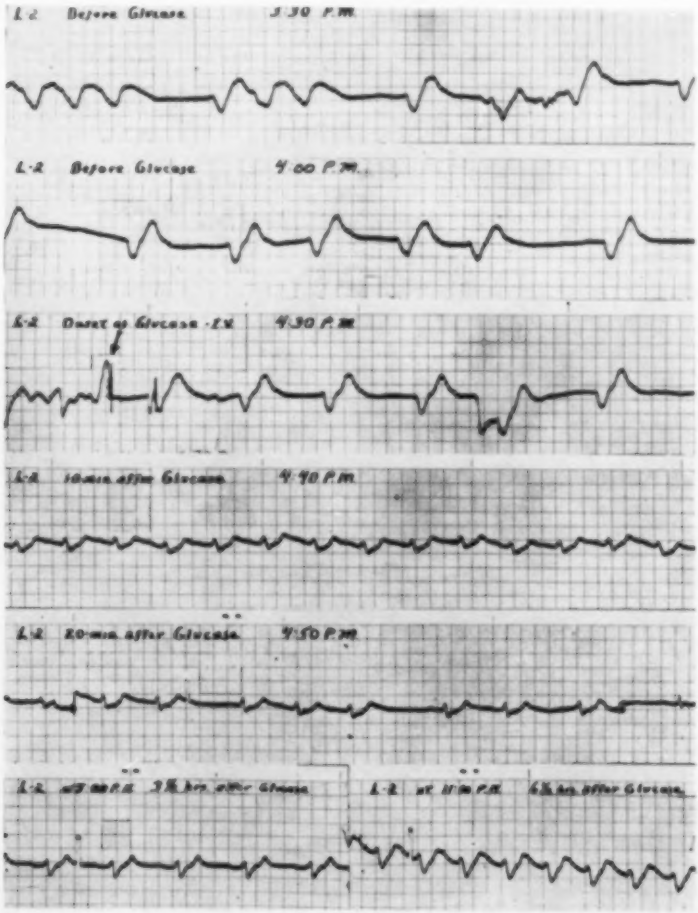


FIGURE 3: The progressive response to intravenous glucose and insulin at the time. The fourth and fifth strips show A-V dissociation with more normal ventricular complexes. Sinus mechanism was established after three and one-half hours of glucose and insulin administration.

potassium. Peaked T waves are noted in V3 and V4; the diminution of R wave, absence of P wave, widening of the QRS complex, and merging of the QRS and T into a sine wave, are all demonstrated at this time. Figure 3 shows short sections of Lead II before 1,000 cc. of 10 percent glucose and 40 units of regular insulin were administered, and then at 10 minutes, 20 minutes, three and one-half hours, and six and one-half hours after the start of glucose administration. The reversion to normal rhythm is demonstrated in the electrocardiogram taken the following day (Figure 4), but voltage is considerably reduced. On March 6, 1956, the electrocardiogram was very near in appearance to the one prior to the abrupt rise in serum potassium. Because of the persistence of uremia and anuria, dialysis was again performed on March 6, 1956. The procedure was tolerated well, even though severe acidosis was present. Four hours after termination of the dialysis the patient convulsed, and in the next 10 hours he had 20 more convulsions. The blood pressure rose to 210/100. Magnesium sulfate, heavy intravenous sedation, and hypertonic fluids were used without response, and he expired on March 7, 1956. Post mortem examination demonstrated the renal findings seen with acute glomerulonephritis.

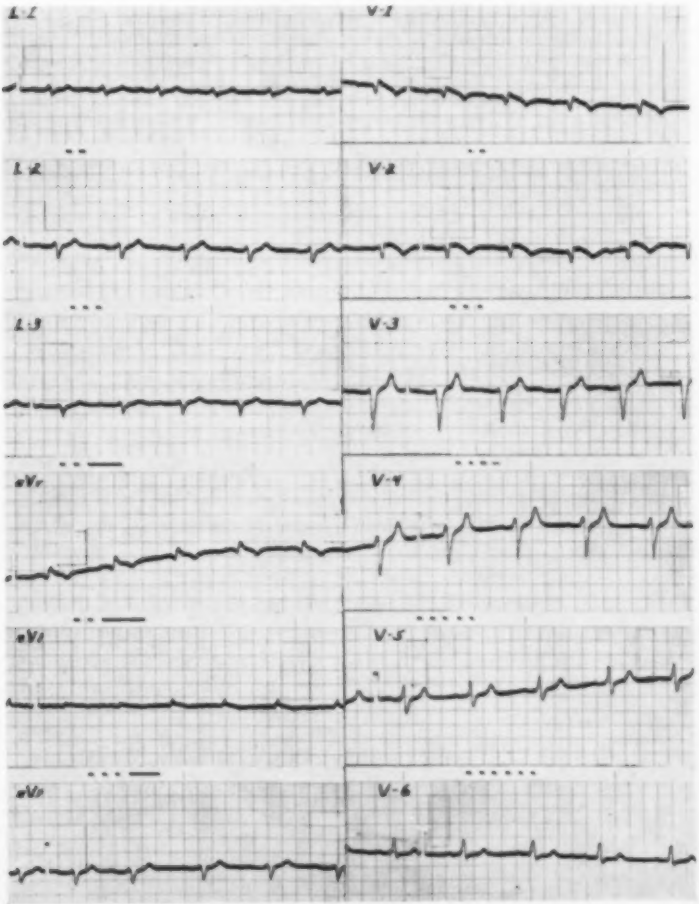


FIGURE 4: Tracing taken on succeeding day. Persistence of sinus mechanism with delayed A-V conduction and low voltage.

Treatment Differential

The management of this case presented several problems, of which the control of hyperkalemia is frequently the most difficult. Unfortunately, there is no specific treatment for the primary pathology in acute glomerulonephritis; but the complications of uremia, acidosis, and hyperkalemia which produce the fatality can frequently be controlled.

The aim of current therapy is to forestall these complications while waiting for the kidney to resume its normal functions. Finch,[10] Meroney,[11] and their associates demonstrated that temporary lowering in serum potassium can be accomplished by the use of simple physiological saline solution. They point out that the addition of calcium, particularly when serum levels of this ion are concomitantly depressed, further aids by directly antagonizing the effects of potassium on the heart muscle. Danowski[12] and Elkinton[13] report the successful reduction of serum potassium through the use of cation exchange resins. Employment of various dialysis techniques has been demonstrated by Kolff.[14] In our case the MacNeill blood dialyzer,[15] which is of unique design and highly effective function, was used in the later stages of the illness.

Recently the use of carbonic anhydrase has been described by Mosely.[16] The resultant decrease of available hydrogen ion without blockage of potassium ion transfer from intracellular position in the renal tubules to the tubule lumen, increases potassium excretion in the urine. The favorable response of patients with hyperpotassemia to exchange transfusion technique has been reported by Goldbloom.[17]

Bellet and associates[18] have shown the effectiveness of molar sodium lactate in the control of heart block secondary to hyperkalemia as well as to other etiologies. The mechanism of action is still under investigation. The current concept is that return of abnormal electrolyte patterns to a more physiological state results in an increase in cardiac rhythmicity.

The use of hypertonic glucose and insulin was initially demonstrated by Darrow[19] and again more recently by Goldbloom.[17] The net effect is the deposition of glycogen similar to that occurring in the treatment of diabetic acidosis. Concurrently potassium is transferred into the cell at a rate that Darrow[19] estimated at 0.36 millimoles of potassium per gram of glycogen. The insulin acts to stimulate the deposition of glycogen, though it is not considered to have a specific potassium reducing effect in itself. The latter form of therapy was used to correct the cardiac arrhythmias in this case.

REFERENCES

1 Winkler, A. W., Hoff, H. E. and Smith, P. K.: "Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride," *Am. J. Physiol.*, 124:478, 1938.

2 Chamberlain, F. L., Scudder, J. and Zwemer, R.: "Electrocardiographic Changes Associated with Experimental Alterations in Blood Potassium in Cat," *Am. Heart J.*, 18:458, 1939.

3 Levine, H. D., Merrill, J. P. and Somerville, W.: "Disturbance of Cardiac Mechanism in Potassium Intoxication," *Circulation*, 3:889, 1951.

4 Herndon, R. F., Meroney, W. H. and Pearson, C. M.: "The Electrocardiographic Effects of Alterations in Concentration of Plasma Chemicals," *Am. Heart J.*, 50: 188, 1955.

5 Currens, J. H. and Crawford, J. D.: "The Electrocardiogram and Disturbances of Potassium Metabolism," *New England J. Med.*, 243:843, 1950.

6 Steward, H. F., Sheppard, E. M. and Horger, E. L.: "Electrocardiographic Manifestations of Potassium Intoxication," *Am. J. Med.*, 6:828, 1948.

7 Keith, N. M., Burchell, H. B. and Baggenstoss, A. N.: "Electrocardiographic Changes in Uremia Associated with High Concentration of Serum Potassium," *Am. Heart J.*, 27:817, 1944.

8 Burch, G. E. and Windsor, T.: *A Primer of Electrocardiography*, Lea and Febiger, 1956.

9 Tarail, R.: "Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances," *Am. J. Med.*, 5:828, 1948.

10 Finch, C. A., Sawyer, C. G. and Flynn, J. J.: "The Clinical Syndrome of Potassium Intoxication," *Am. J. Med.*, 1:337, 1946.

11 Meroney, W. H. and Herndon, R. F.: "The Management of Acute Renal Insufficiency," *J.A.M.A.*, 155:877, 1954.

12 Danowski, T. S., et al.: "The Use of Cation Exchange Resins in Clinical Situations," *Ann. Int. Med.*, 35:529, 1951.

13 Elkinton, J. R.: "Treatment of Potassium Retention in Uremia with Cation Exchange Resins," *Am. J. Med. Sc.*, 220:547, 1950.

14 Kolff, W. J.: "Serum Potassium in Uremia," *J. Lab. Clin. Med.*, 36:727, 1950.

15 MacNeill, A. E., Doyle, J. E., Witebsky, E. and Swanson, P. R.: "Unusual Hemolytic Transfusion Reaction with Renal Failure Treated by Hemodialysis," *J.A.M.A.*, 161:1630, 1956.

16 Mosely, V.: "The Use of Carbonic Anhydrase Inhibitor in the Treatment of Hyperkalemia," *J. Am. Geriat. Soc.*, 4:58, 1956.

17 Goldbloom, R. B.: "Renal Failure with Extreme Hyperpotassemia," *New England J. Med.*, 250:717, 1954.

18 Bellet, S. and Wasserman, T.: "Indications and Contraindications for the Use of Molar Sodium Lactate," *Circulation*, 15:591, 1957.

19 Darrow, S. C.: "Blood Fluid Physiology: Role of Potassium in Clinical Disturbance of Body Water and Electrolyte," *New England J. Med.*, 242:1014, 1950.

A Large Pseudoaneurysm Caused by Extrapleural Plastic Ball Plombage

MASASHICHI KAWANO, M.D., F.C.C.P., SOROKU SAHEKI, M.D.*
and YUZABURO MURATA, M.D.**

Nagasaki, Japan

Collapse therapy of pulmonary tuberculosis by means of plastic plombage is now out of use except in a few clinics or with radical modification. Reasons for this abandonment are a series of complications some of which have led the patients to unhappy outcomes. We have recently met with one of these situations and thought it worthwhile to report it here.

Clinical History: The patient was a 32-year-old man who had been diagnosed as having a tuberculous lesion in his left upper lobe in 1949 and underwent collapse surgery using several plastic balls of larger size at the University Hospital on December 27, 1949. He had not noticed subjective symptoms until July 20, 1956, when he felt a sudden pain and pressure inside his left chest wall after elevation of his left arm. Slight fever, and coughing, without expectoration, lasted for a few days but no pulmonary hemorrhage, or blood-streaked sputum, was noticed. He visited our hospital asking for removal of the plastic balls. We hesitated to operate on him immediately and watched him carefully, for the fever between 99 and 101° F. persisted for a long period. While we were still pondering on the indication of removal of plastic balls in this condition, hemoptysis started on August 8, 1956 and within a few days it changed into a profuse hemorrhage exceeding 500 cc. on the night of August 25th. The hemorrhage reached 1,000 cc. the next night and he complained of a severe chest pain which was hardly controlable by injection of large doses of demerol, and he requested immediate thoracotomy and removal of the balls.

Operation: He was subjected to thoracotomy on August 31, 1956. To combat the pulmonary hemorrhage during operation, he was placed in the face-down position, using the table specially built for this purpose. For the same reason regional anesthesia was preferred to general anesthesia, in which preservation of tracheal reflex and maintainance of air-way is a hazardous problem. The regional anesthesia was reinforced by intramuscular administration of M_1 cocktail consisting of Chlorpromazine 50 mg., Demeral 105 mg. and Prometazine 50 mg. one hour prior to operation.

Three ribs, third, fourth and fifth, were resected following skin incision and division of muscles. Then the thorax was entered through the 5th periosteal bed. Adhesion of the lung to the wall was so severe that detachment required a meticulous manipulation. The lower lobe was almost intact but the upper lobe was compressed to the wall by the pressure from inside. When the hematoma at the lateral edge of the upper lobe was partly removed oozing of blood was met and a gauze pack was placed to control the oozing. The medial-posterior approach was taken next and the thick white pleura at the upper end of the compact upper lobe was incised. Before long a part of a ball surface was disclosed and the ball was extracted with a large clamp. No sooner than the removal, a torrent of arterial blood filled the chest. The operator quickly probed the upper space and floating balls were all extracted in a moment. A large amount of gauze packing was placed in the chest to control the bleeding, and the wound was closed in layers with interrupted silk sutures without delay. The blood loss was at this time 2,000 cc., systolic pressure around 40 mg. Hg., and the patient was unconscious. Treatment with generous transfusion of bank blood and fresh blood, and administration of vasospastics and other drugs helped the patient to overcome the shock stage, and he survived.

The second operation was undertaken a week later. This time the patient was put under general anesthesia with intratracheal intubation, for absence of pulmonary hemorrhage during operation and postoperative days convinced the anesthetist of the safety of this method. We presumed that the bleeding point was in the upper pulmonary vessels. The chest was reopened through the old wound and without removing the gauze pack the lower lobe was mobilized to ease the intrathoracic

*From the Department of Surgery (Director: Prof. Hideo Tsujimura), Nagasaki University School of Medicine.

**From the Department of Radiology (Director: Prof. Hiroshi Tachiiri), Nagasaki University School of Medicine.

maneuver. Then, the hilum was approached from behind. The upper bronchus was exposed and treated after Sweet's method. Dissection of individual vessels seemed difficult, and the remaining hilum structure was ligated together temporarily and the gauze pack was removed one after one. Another massive bleeding of arterial blood succeeded the procedure and further operation was abandoned. The patient again survived the operation but blood seepage from the wound persisted amounting to over 400 cc. a day.

Angiography: To identify the bleeding point, the patient had an angiocardiogram done by the Department of Radiology. The reported findings were as follows:

"The angiogram taken immediately after injection of 76% Urographine 50 cc. through the right saphenous vein reveals no abnormal finding in the right atrium and ventricle, although the trachea, vena cava, and heart are tracted to the right, and posterior portion of the left upper ribs were absent. Lack of filling in the left upper artery is likely due to ligature of the artery at the previous operation.

Angiogram taken four seconds after the injection (Fig. 2) also shows no abnormal findings of the left atrium and ventricle, aortic arch, ascending and descending aorta. Filling of both common carotid arteries, vertebral arteries, and subclavian arteries seem to be normal, but the left subclavian artery shows insufficient contrast in comparison with the right. An unusual finding is in the vault of the left thorax where lies a round or oval homogeneous shadow of clear smooth outline spreading from the upper border of the second rib to the fourth rib. No leakage of the contrast agent was recognized even at the divided end of the intercostal arteries.

Angiogram taken six seconds after the injection (Fig. 3) shows the presence of the above-mentioned round shadow even when contrast agent in other arteries has disappeared, but this shadow also disappeared completely in 30 minutes.

From these findings this round shadow is suspected to be a large aneurysm having communication with the left subclavian or common carotid artery. It is a regret that the lateral angiogram was not available because of difficulties with the apparatus and patient. But it can be learned from the postero-lateral film that the aneurysm had arisen from the subclavian artery which is not filled so well as the common carotid artery. The hemorrhage in patient's history is attributable to this aneurysm which shows homogeneous, smooth and round contour suggesting a relatively fresh aneurysm with incomplete organization."

Autopsy: Three days later in the afternoon, the patient died suddenly following a severe cough and convulsion. Orotracheal suction, and adrenalin injection failed to alter his course.

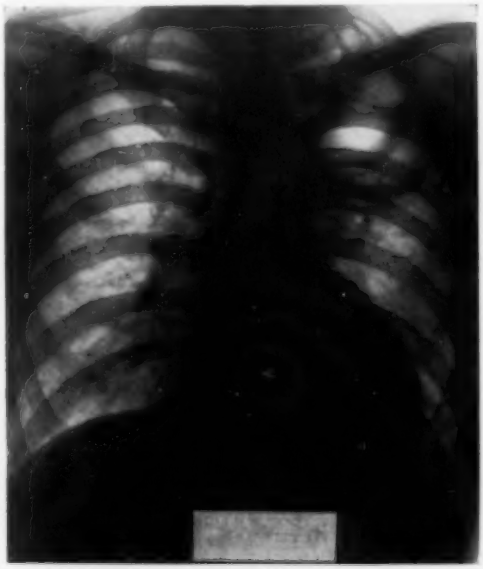


FIGURE 1: Preoperative x-ray film.

Postmortem examination revealed a large sac communicating with the subclavian artery as indicated by angiograms (Fig. 3). The sac was filled with blood and lined by fibrinous membrane of many layers without any vessel wall structure. Apparently this is a pseudo-aneurysm formed by repetition of bleeding, and coagulation process.

The space between the pseudoaneurysm and the lung was filled with clotted blood, and the adjoining visceral pleura had a large defect. There was found no active lesion in the upper lobe but an old partially calcified fibrous lesion. No possible source of profuse hemorrhage such as cavitation or bronchial ulceration was discovered in any lobe. The trachea was filled with mass of clotted blood at the lower end as were the openings of the main bronchi, and the stump of the left upper bronchus had suppurative change and was partially torn.

Discussion

It is clear from the clinical and postmortem findings that the round edge of a plastic ball adjacent to the subclavian artery gave continuous pressure against the vessel wall for nearly seven years and gradually eroded the anemic necrotized wall structure and finally perforated it. This was followed by bleeding which caused the chest pain and feeling of pressure, and a pseudoaneurysm had grown there. But high arterial pressure did not allow the closure of the perforation and bleeding was repeated, leading to a high pressure in the collapsed space which was in contact with the pathologic lung surface, and gave the outlet for the bleeding through the bronchial route, thus causing preoperative pulmonary hemorrhage. The first operation lessened the pressure in the space by removing the plastic balls. The bleeding was stopped by gauze pack only temporarily. We should have done an angiocardiogram on the patient before the second operation, but the condition of the patient made us hesitate to do it, and we had in mind the pulmonary vessels under the pressure of the ball as the main source of hemorrhage. Thus, we operated the second time, successfully removing the upper lobe, but failed in treating the real source of bleeding. This continued, or even increased following the second operation, and finally pressed into

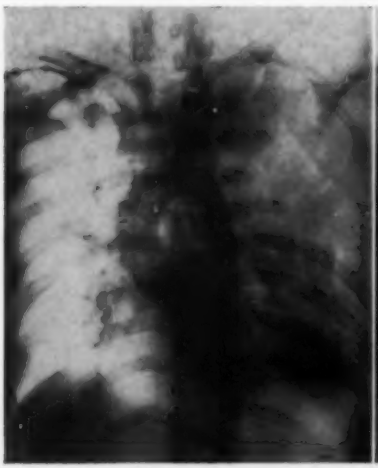


FIGURE 2

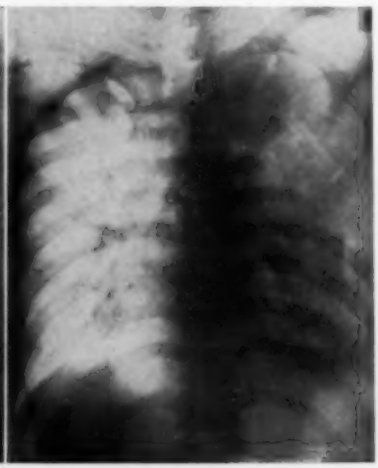


FIGURE 3

Figure 2: Four seconds after angiographic injection. *Figure 3*: Six seconds after injection.

the bronchial stump, which was already infected, and yielded easily to the pressure, giving way to the flow of blood into the trachea and consequent asphyxia.

The most common complication of plastic plombage has been the perforation of cavity wall, and subsequent empyema. Little attention has been given to the danger of perforation of important intrathoracic vessels. This is unlikely to occur in a short duration after the operation but, if once started, is very difficult to control in time, unless the surgeons, as well as patients, are alert enough to find out this possible danger at an early stage.

We think it is safer to remove the plastic balls as early as possible, if the balls are already in the thorax. We believe plastic plombage as a treatment of pulmonary tuberculosis is an unadvisable procedure except in a few selected cases. Our case teaches us that it is a necessary safeguard against severe complications to substitute for plastic plombage pulmonary resection, or thoracoplasty, even though the patient with plombage does not have any complaint.

The authors wish to acknowledge the collaboration of the Department of Radiology headed by Prof. Hiroshi Tachiiri and the Department of Pathology headed by Prof. Shigeru Matsuoka and the suggestion and advices given by Prof. Hideo Tsujimura and Assistant Prof. Takashi Hirai of the Department of Surgery.

BIBLIOGRAPHY

Goto, S. et al: "Postmortem Examination of Seven Cases Died After Extrapleural Plastic Ball Plombage," *Jap. J. Thoracic Surg.*, 6:372, 1953.

Inada, K. et al: "An Evaluation of Extrapleural Pneumonolysis With Filling With Plastic Balls," *J. Thoracic Surg.*, 27:503, 1954.

Kai, Taro et al: "Follow-up of 80 Cases of Extrapleural Pneumonolysis With Plastic Ball Plombage," *Jap. J. Thoracic Surg.*, 3:341, 1950.

Koshimizu, T. et al: "Clinical Symptoms Following Extrapleural Plastic Ball Plombage," *Jap. J. Thoracic Surg.*, 3:212, 1950.

Laird and Stephans: "Plombage; Review and Report on Use of Polystan," *Tubercle*, 24:68, 1953.

Lewin and Aronsvitch: "Changing Indications for Collapse Therapy," *Canad. M. A. J.*, 69:481, 1953.

Nagaishi, C. et al: "Application of Plastic for the Treatment of Pulmonary Tuberculosis and Extrapleural Pneumonolysis with Filling of Plastic Balls," *Kekkaku-Kenkyu*, 3:38, 1947.

Nagaishi, C.: "Analytical Studies on the 'Failure' of Extrapleural Pneumonolysis with Filling of Plastic Balls," *Annals of Tuberculosis* (Jap. publication), 1: No. 3, 134, 1950.

Sawazaki, Hiroji et al: "An Evaluation of 148 Cases of Extrapleural Pneumonolysis with Plastic Ball Plombage," *Jap. J. Thoracic Surg.*, 3:117, 1950.

Sawazaki, Hiroji: "Result in 1064 Cases of Extrapleural Lucite Plombage in 40 State Sanatoriums," *Iryo*, 4:95, 1950.

Sawazaki, Hiroji: "Plastic Resin Plombage Examined from the Standpoint of Sputum Conversion and Complications," *Jap. J. Thoracic Surg.*, 5:8, 1952.

Takatsuka, Fujio: "Failures and Complications of Extrapleural Lucite Plombage," *Jap. J. Thoracic Surg.*, 3:281, 1950.

Trent, J. C. et al: "An Evaluation of Extrapleural Pneumonolysis with Lucite Plombage," *J. Thoracic Surg.*, 18:175, 1948.

Wilson, D. A.: "Extrapleural Pneumonolysis with Lucite Plombage," *J. Thoracic Surg.*, 17:11, 1948.

Woods, F. M. et al: "Extraperiosteal Temporary Plombage in Thoracoplasty," A Preliminary Report, *Dis. Chest*, 18:401, 1950.

Yada, H.: "Complications Following Extrapleural Pneumonolysis with Plastic Ball Plombage," *Jap. J. Thoracic Surg.*, 5:317, 1952.

Yasuoka, H.: "Extrapleural Plombage with Plastic Balls," *Jap. J. Thoracic Surg.*, 2:119, 1949.

Yasuoka, H. et al: "Failures and Complications of Extrapleural Plombage with Plastic Balls," *Jap. J. Thoracic Surg.*, 2:233, 1949.

Bilateral, Primary, Simultaneous Bronchogenic Carcinoma

Presentation of a Case

E. CATO DRASH, M.D., F.C.C.P. and RICHARD N. DE NIORD, JR., M.D.
Charlottesville, Virginia

The question of the multicentric versus the unicentric origin of bronchogenic carcinoma is as yet undecided. Some observers believe that multiple sites of metaplastic epithelium or preinvasive carcinoma (carcinoma in situ) may exist asymptomatically throughout the bronchial tree.[1-3] Auerbach has demonstrated the ubiquitous changes of hyperplasia, metaplasis and early neoplastic manifestations which appear in the pulmonary mucosa in some cases. He has also shown that, in general, there are four types of metaplastic changes present in the lungs of individuals with bronchigenic carcinoma—1) basal cell hyperplasia, 2) stratification, 3) squamous metaplasia, and 4) carcinoma in situ. At some point in the biological maturity of lung cancer, one of these sites attains autonomy and the atypical growth of lung cancer continues. The term "bronchogenic carcinoma" used here refers to the description of Liebow[5], and includes a) epidermoid carcinoma; b) anaplastic carcinoma; and c) adenocarcinoma. The alveolar cell carcinoma has a diffuse form not discussed at this time. An excellent study of multiple sites of atypical bronchial epithelium was made 20 years ago by Lindbert[6]. McGrath[7] has added weight to the multicentric site theory, by demonstration of multicentricity in 54 of 87 lungs containing bronchogenic carcinoma. Numerous observers have described multiple pulmonary "carcinomas in situ,"[8] but few have actually visualized or described simultaneous bilateral invasive bronchogenic carcinoma. Invasion signifies autonomy, and usually occurs unilaterally. Because of its unusual occurrence, we are presenting one case of bilateral, primary, simultaneous bronchogenic carcinoma.

This 52 year old white man was admitted to the University of Virginia Hospital with a three month history of increasing fatigability, 22 pound weight loss, cough, wheezing, and left chest pain. No previous diagnostic studies had been performed prior to admission. He smoked two packs of cigarettes per day for approximately 25 years. Physical examination revealed diminished breath sounds over the left chest with some inspiratory wheezing and emaciation. *X-ray* film demonstrated left hilar adenopathy, and a 2 cm. nodule in the left apex.

Discussion

Ever increasing evidence points to the multicentric origin of bronchogenic carcinoma. Numerous sites of atypical metaplasia or carcinoma in situ have been repeatedly demonstrated. These sites are grossly unremarkable and probably do not account for positive cytological studies.[9] Besides the possibility of morphologic defects,[10] or developmental abnormalities[11] causing multicentricity, it would seem logical to assume that bronchial irritants effect the entire tracheo-bronchial mucosa and not a single re-

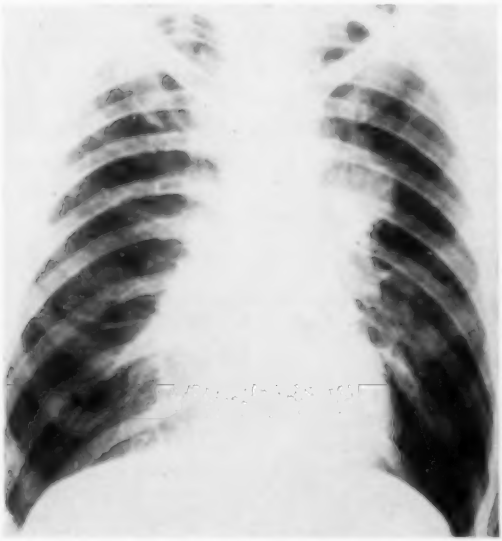


FIGURE 1: *Bronchoscopy—Right Side:* Small one-half cm. discrete, pale granular mass was present just distal to the upper lobe orifice. The remainder of the right bronchial tree was negative. *Left Side:* A constricting, annular mass was seen in the left main stem bronchus at a level 2 cm. from main carina and almost completely obstructing the lumen. This lesion was also pale, discrete and bled easily on biopsy.

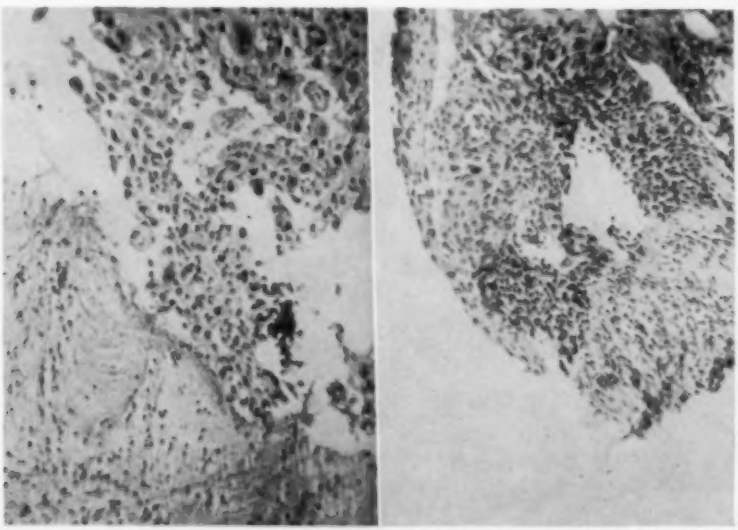


FIGURE 2 FIGURE 3

Figures 2 and 3: ***Microscopic:*** **Figure 2 represents biopsy of the right and Figure 3 biopsy of the left endobronchial lesions. Both lesions show typical invasive epidermoid carcinomas.**

stricted site. Once growth and autonomy has occurred in one area, this site progresses at a variable growth rate. It is interesting to note that only rarely does another area of metaplasia in the same lung (or other lung?) develop frank invasive characteristics. This appears as a form of growth suppression in the remaining metaplastic areas once invasion and autonomy have occurred.

REFERENCES

1 Black, H. and Ackerman, L. L.: "The importance of epidermoid carcinoma in situ in the histogenesis of carcinoma of the lung," *Am. Surg.*, 136:77, 1952.

2 Broders, A. C.: "Carcinoma in situ contrasted with benign penetrating epithelium," *J.A.M.A.*, 99:1070, 1932.

3 Peterson, A. B., Hunter, W. C. and Sneeden, D.: "Histological study of five minute pulmonary neoplasms believed to represent early bronchogenic carcinoma," *Cancer*, 2:991, 1949.

4 Auerback, Oscar et al: "Changes in the bronchial epithelium in relation to smoking and cancer of the lung," *The New Eng. Jour. Med.*, 256:97, 1957.

5 Liebow, A. A.: "Tumor of the lower respiratory tract," *Fasicle*, 17.

6 Lindberg, K.: "Uber die Histologic des primaren lungen Krebses," Arbeiten aus dem path. Institut der Universität, *Hersingfors*, 8:225, 1935.

7 McGrath, E. J. et al: "Bronchogenic carcinoma, a product of multiple sites of origin," *J. Thor. Surg.* 24:271, 1952.

8 Ryan, Robert F., McDonald, John M.: "Bronchogenic carcinoma with in situ carcinoma in the opposite lung," Report of five cases. Proceedings of the staff meetings of the Mayo Clinic, 31:478, 1956.

9 Liebow, A. A., Lindskog, G. E. and Blower, W. D.: "Cytological studies of sputum and bronchial secretion in the diagnosis of cancer of the lung," *Cancer*, 1:223, 1948.

10 Mulligan, E. M. and Harper, Fred R.: "The morphology of primary carcinoma of the human lung," *J. Thor. Surg.*, 12:734, 1943.

11 Womack, Nathan, A. and Graham, Evarts, A.: "Developmental abnormalities of the lung and bronchogenic carcinoma," *Arch Path.*, 34:301, 1942.

Editorial

War — A Disease

Sweden is a small country and though its earlier history is full of war, it has now lived in peace for almost 150 years. Our own history, like our experiences in the shadow of two World Wars, has taught us that war never pays, not even for the victor. Wars lead only to new wars, with all its accompanying human suffering. War is a disease, a disease not of individuals, but of countries. It can be acute, flaring up quickly and soon over. More often, it is chronic and spreads like a plague, constantly involving new countries and ultimately threatening—as it does now—the existence of the entire world. We all know that chaos threatens, that the latest technical advances have produced weapons which can exterminate great sections of the population—even place in jeopardy the existence of every living being on this planet. Everything that can be done to prevent such a development must be done—and quickly. Somehow or other, nations much reach an agreement. The cold war must be brought to an end and the world once more restored to peace, a true peace.

All this is simple enough to say, perhaps especially so for us doctors whose mission is to heal, not to destroy. To this end, we increase our knowledge, seek experience at national and international congresses and convert this knowledge into deeds. We support and participate in the efforts to raise the living standards of our populace. We successfully combat epidemics. We detest war not only because it destroys everything that has been built with so much effort, but, above all, because of what it costs in human suffering. For these reasons, we gladly participate in the Doctors' Crusade for Peace.

In the campaign against war as a disease of nations, the same means have been employed as we ourselves use in our work as doctors, although naturally on a much greater scale. The generous aid which the United States of America has given to underdeveloped and needy countries cannot be too highly praised. It contributes to a higher living standard, provides opportunities for work and thus enhances the will to live. At the same time, it increases resistance against physical and psychic infections of various kinds. Of corresponding importance is the aid given to countries in their campaign against diseases. Other and stronger medicines are needed, and the doctors for this are our statesmen on whom rests a heavy responsibility, all the more so as it may now be a question of life or death for every one of us. We look with hope to the United Nations where all the threads meet. Let us trust that success will be achieved here in solving the difficult problem of welding all nations together into unity so that the world may at last gain what it has so long yearned for—enduring peace.

*Erik Hedvall, M.D., F.C.C.P.**
Uppsala, Sweden

*Governor of the College for Uppsala, Sweden.

FIFTH INTERNATIONAL CONGRESS
ON
DISEASES OF THE CHEST

The Council on International Affairs of the American College of Chest Physicians takes pleasure in announcing the following schedule of activities in connection with the Fifth International Congress to be held in Tokyo, Japan, September 7-11, 1958. All arrangements for the Congress have been made with the cooperation and generous assistance of the College officials in Japan.

Saturday, September 6

9:00 a.m.—Registration	DAIICHI BUILDING
10:00 a.m.—Opening Executive Session Regents and Governors	TOKYO KAIKAN
12:00 noon—Luncheon Meeting, Editorial Board "Diseases of the Chest"	TOKYO KAIKAN
2:00 p.m.—International Committee Meetings	TOKYO KAIKAN

Sunday, September 7

9:00 a.m.—Registration	DAIICHI BUILDING
8:30 p.m.—Inaugural Ceremony and Convocation	YOMIURI HALL

Monday, September 8

8:00 a.m.—Registration	DAIICHI BUILDING
9:00 a.m.—Scientific Sessions	DAIICHI BUILDING
2:00 p.m.—Scientific Sessions	DAIICHI BUILDING
6:00 p.m.—Reception by Hon. Nobusuke Kishi, Prime Minister, at his official residence	

Tuesday, September 9

8:00 a.m.—Registration	DAIICHI BUILDING
9:00 a.m.—Scientific Sessions	DAIICHI BUILDING
2:00 p.m.—Scientific Sessions	DAIICHI BUILDING
Evening —Embassy Receptions by invitation for delegates from respective countries	

Wednesday, September 10

8:00 a.m.—Registration	DAIICHI BUILDING
9:00 a.m.—Scientific Sessions	DAIICHI BUILDING
2:00 p.m.—Scientific Sessions	DAIICHI BUILDING
8:00 p.m.—Congress Banquet	TOKYO KAIKAN

Thursday, September 11

8:00 a.m.—Registration	DAIICHI BUILDING
9:00 a.m.—Scientific Sessions	DAIICHI BUILDING
12:00 noon—Luncheon Meeting, Closing Executive Session, Regents and Governors	TOKYO KAIKAN
2:00 p.m.—Fireside Conferences	TOKYO KAIKAN
6:00 p.m.—Reception by Mr. Seiichiro Yasui, Governor of Tokyo, at Chinzanso	

September 8-11

Motion Picture Sessions	DAIICHI BUILDING
Exhibits—Technical and Scientific	RED CROSS BUILDING

Ladies Activities
Fifth International Congress

Sunday, September 7

8:30 p.m.—Inaugural Ceremony and Convocation — YOMIURI HALL

Monday, September 8

10:00 a.m.—Tour of Tokyo

2:00 p.m.—Tour of Tokyo

6:00 p.m.—Reception by Hon. Nobusuke Kishi, Prime Minister, at his official residence

Tuesday, September 9

10:00 a.m.—Kimono Fashion Show — TAKASHIMAYA DEPARTMENT STORE

2:00 p.m.—Flower Arrangement Demonstration — SOGETSU KAIKAN

Wednesday, September 10

9:00 a.m.—4:30 p.m.—Bus Tour to Kamakura and Enoshima (including lunch)

8:00 p.m.—Congress Banquet — TOKYO KAIKAN

Thursday, September 11

10:00 a.m.—Fashion Show — MITSUKOSHI DEPARTMENT STORE

2:00 p.m.—Tea Ceremony — CHINZANSO

6:00 p.m.—Reception by Mr. Seiichiro Yasui, Governor of Tokyo, at Chinzanso

24TH ANNUAL MEETING

The 24th Annual Meeting of the American College of Chest Physicians was held at the Fairmont Hotel, San Francisco, June 18-22; the meeting was very successful with a registration of more than 1400 physicians and guests representing 46 of the States and a dozen other countries and territories. Twenty-five technical exhibits, the maximum number that could be accommodated, were on display throughout the meeting.

Fellowship Certificates were awarded to 160 physicians at the Annual Convocation of the College held on Saturday, June 21. Dr. Donald R. McKay, Buffalo, New York, incoming President of the College, addressed the Convocation assembly.

The Convocation was followed by the Annual Presidents' Banquet which was attended by 495 physicians and members of their families. A cocktail party, sponsored by the Panray Corporation of New York City, preceded the banquet. Dr. Burgess L. Gordon, Albuquerque, New Mexico, President of the College, presided at the banquet and introduced the officials and special guests.

Dr. Walter B. Brown, Livermore, California, Chairman of the Committee on Prize Essay Awards, introduced the first and second prize winners of the 1958 Essay Contest of the College. First prize winner was Eugene Friedberg of the University of Buffalo, Buffalo, New York, who was presented with a certificate and a cash award in the amount of $500.00 for his essay "Murmur Production in Aortic Stenosis: An Analysis Using a Hydraulic Model." Ronald J. O'Reilly of the University of California at Los Angeles, received the second prize certificate and a cash award of $300.00 for his essay entitled "Clinical Recognition of Carbon Dioxide Intoxication." The third prize winner was Alan S. Deutsch of the New York University College of Medicine, New York City, who was unable to be present. Mr. Deutsch received his certificate and award of $200.00 at a special presentation ceremony in New York arranged by Dr. Coleman B. Rabin, Governor of the College for New York State. The com-

mittee awarded Honorable Mention and a prize of $50.00 to Miss June Hagen of the University of Cape Town Medical School, Cape Town, South Africa, for her excellent essay "Cryptococcosis of the Lung." The award was presented to Miss Hagen by Dr. David P. Marais, Regent of the College for South Africa, at a special meeting.

Presentation of the 1958 College Medal was made to Dr. J. Winthrop Peabody, Sr., Washington, D. C., by Dr. Gordon, for meritorious achievement in the specialty of diseases of the chest, particularly in the field of postgraduate medical education. Dr. Peabody has served as Chairman of the Council on Postgraduate Medical Education of the College since its inception in 1946. His photograph and biography appeared in the July issue of *Diseases of the Chest*.

The Immediate Past President of the College, Dr. Herman J. Moersch of the Mayo Clinic, Rochester, Minnesota, presented the Presidential Scroll to Dr. Gordon and the College Past-President's Pin to Mrs. Gordon.

Announcement was made of the approaching Fifth International Congress on Diseases of the Chest, to be held in Tokyo, Japan, September 7-11, under the sponsorship of the Council on International Affairs of the College. Through the kindness of Japan Air Lines, favors were distributed to the guests by two lovely girls wearing Japanese kimonos.

A Homecoming Meeting to be held in Albuquerque, New Mexico in October, 1959, in celebration of the 25th anniversary of the first College meeting, was announced at the banquet. A number of members from Albuquerque and their wives, dressed in typical Western style, distributed favors by courtesy of the Albuquerque Chamber of Commerce.

The evening closed with a dance sponsored by the California Chapter of the College.

Administrative Meetings

The annual meetings of the Executive Council, Board of Regents and Board of Governors were held in San Francisco where reports from the various councils and committees were received, and matters of policy discussed. The proceedings of these meetings and reports of councils and committees will be published in subsequent issues of the College journal.

On Saturday morning, June 21, the Open Administrative Session was held and reports were presented by the Treasurer, the Historian, the Executive Director and the Committee on Nominations. The following officers, Regents and Governors were elected:

Officers

President.	Donald R. McKay, Buffalo, New York
President-Elect:	Seymour M. Farber, San Francisco, California
1st Vice-President:	M. Jay Flipse, Miami, Florida
2nd Vice-President:	Hollis E. Johnson, Nashville, Tennessee
Treasurer:	Charles K. Petter, Waukegan, Illinois
Asst. Treasurer:	Albert H. Andrews, Chicago, Illinois
Chairman, Board of Regents:	John F. Briggs, St. Paul, Minnesota

Regents

District No. 2:	Edgar Mayer, New York, N. Y.
District No. 4:	Dean B. Cole, Richmond, Virginia
District No. 6:	Howard S. Van Ordstrand, Cleveland, Ohio
District No. 9:	David H. Waterman, Knoxville, Tennessee
District No. 10:	Arthur M. Olsen, Rochester, Minnesota
District No. 14:	Edward H. Morgan, Seattle, Washington
District No. 17:	Thomas G. Heaton, Toronto, Canada
Historian:	Carl C. Aven, Atlanta, Georgia

Governors:

Delaware:	Gerald A. Beatty, Wilmington
Indiana:	Jerome V. Pace, Rockville
Iowa:	William B. Bean, Iowa City
Kentucky:	John S. Harter, Louisville
Massachusetts:	Norman J. Wilson, Boston
Montana:	Lloyd M. Taylor, Great Falls
Nebraska:	Max Fleishman, Omaha
Nevada:	Robert C. Locke, Reno
New Hampshire:	Francis J. Kasheta, Glencliff
New Mexico:	Joseph E. J. Harris, Albuquerque
Ohio:	Ray W. Kissane, Columbus
Oklahoma:	Donald W. McCauley, Okmulgee
Oregon:	William S. Conklin, Portland
Rhode Island:	Frank A. Merlino, Providence
South Carolina:	J. Gordon Seastrunk, Columbia
South Dakota:	Robert C. McCroskey, Rapid City
Tennessee:	Duane Carr, Memphis
Wisconsin:	Mischa J. Lustok, Milwaukee

Announcement was also made that the Interim Session of the College would be held at the Mayo Clinic, Rochester, Minnesota on November 29 and 30, 1958. An outstanding scientific program, including formal papers, panel discussions, round table luncheons and fireside conferences, is now being organized by the program committee for the meeting. Tours of the Clinic and an interesting display of scientific and technical exhibits will also be included. The Board of Governors will hold its semi-annual meeting in Rochester on Saturday, November 28, and examinations for Fellowship, as well as meetings of various councils and committees will be held on that day.

On Monday, December 1, the Board of Regents will hold its semi-annual meeting at the Radisson Hotel, Minneapolis. A dinner and evening scientific session is also planned. The Clinical Meeting of the American Medical Association will be held in Minneapolis, December 2 through 5, 1958.

It was announced that the 25th Annual Meeting, Silver Anniversary, of the American College of Chest Physicians, would be held in Atlantic City, New Jersey, June 3-7, 1959. A number of special functions are being planned to celebrate the Silver Anniversary Meeting of the College.

Ladies Activities

The ladies attending the 24th Annual Meeting of the College enjoyed a delightful program of activities arranged for them by Mrs. Seymour M. Farber and the members of her committee. On Thursday, June 19, the ladies were taken to the Alta Mira Hotel in Sausalito for lunch, and from there to Jackson Square, one of the oldest sections of San Francisco, where they were taken on a tour of the Interior Decorator Display Shops. A dinner party was arranged for the ladies at the Yamato Sukiyaki House on Friday evening, June 20, while their husbands attended the fireside conferences of the College. Following the Japanese style dinner, a Japanese Fashion Show was presented for the ladies. On Saturday evening, June 21, the ladies attended the Annual Convocation, cocktail party and Presidents' Banquet of the College held at the Fairmont Hotel. Mrs. Farber, Chairman, and Mrs. Roger Wilson, Co-Chairman of the Ladies Committee, as well as the other members of the committee, are commended for the enjoyable program they prepared for the ladies and for the splendid manner in which the activities were handled.

SCIENTIFIC PROGRAM COMMITTEE REQUESTS ABSTRACTS FOR SILVER ANNIVERSARY MEETING

The 25th Annual Meeting of the College will be held in Atlantic City, New Jersey, June 3-7, 1959. Special plans for the scientific program to be presented at the Silver Anniversary Meeting are now under way. Physicians who wish to present papers are urged to submit a 200-word abstract to the appropriate committee chairman at the earliest possible date for consideration. Please forward abstracts to one of the following co-chairmen:

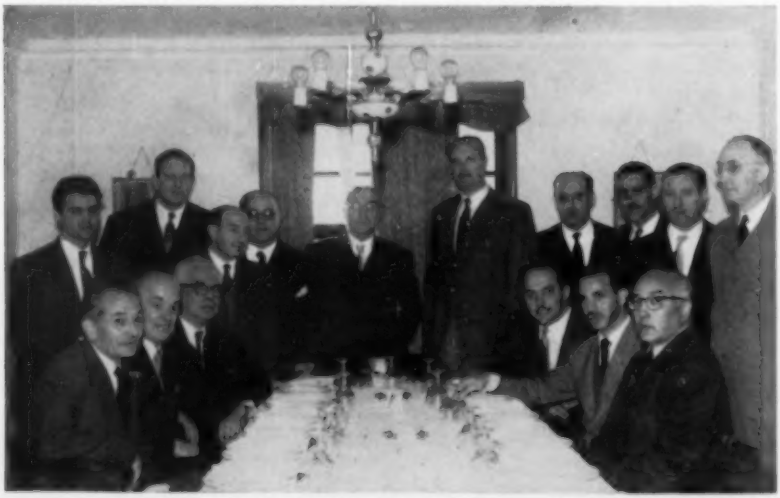
Dr. Arthur M. Master, 125 East 72nd Street, New York City
Chairman, Section on Cardiovascular Diseases
Dr. Coleman B. Rabin, 110 East End Avenue, New York City
Chairman, Section on Pulmonary Diseases

The Committee on Motion Pictures of the College will be interested to learn of new films on diseases of the chest for possible presentation at the 25th Annual Meeting in Atlantic City. All pertinent information concerning films should be forwarded to Dr. Paul H. Holinger, chairman of the committee, 112 East Chestnut Street, Chicago 11, Illinois. The committee will be pleased to review films for official approval and inclusion in the Approved Film List of the American College of Chest Physicians.

College Chapter News

CANARY ISLANDS CHAPTER

The Canary Islands Chapter met at Santa Cruz de Tenerife on January 25, at which time the executive council discussed future chapter activities. Following the business meeting, a panel discussion on the subject "Preparation of the Patient for Thoracic Surgery" was held. Dr. Tomas Cervia, Governor of the College for the Canary Islands, presided at the scientific session. The next meeting of the chapter was held in Las Palmas on May 10 at which a program dealing with "Present Day Treatment of Pulmonary Tuberculosis" was presented.



Member of the Canary Islands Chapter attending the meeting on January 25, 1958. *Seated, left to right*: C. R. Gavilanes, President of the Chapter, José Pérez Pérez, Chapter Treasurer, José Gerardo Martin Herrera, D. Ponce Arencibia, Miguel Cuesta Palomero and José Estrada. *Standing, left to right*: Enrique González, Secretary of the Chapter, Agustin Bosch Millares, V. Navarro Marco, José Domínguez, Tomás Cerviá, Governor, Augusto Mendez de Lugo, J. M. del Arco Montesinos, Vice-President of the Chapter, M. García González, Francisco Pérez Pérez, and Ramon Luelmo.

ANDALUSIAN CHAPTER

Members of the College in Spain met recently to form the Andalusian Chapter. The following officers were elected:

President:	Norberto Gonzales de la Vega, Granada
Vice-President:	Salvador Almansa de Cara, Malaga
Secretary:	Antonio Azpitarte Rubio, Granada
Treasurer:	Carlos Gomez-Moreno, Granada

PANAMANIAN CHAPTER

The Panamanian Chapter of the College met on May 3, 1958 in David, Republic of Panama in conjunction with the Panamanian Association of Phthisiologists. Dr. Maximo Carrizo Villareal, Regent of the College, presented a paper on "Tuberculin Prevention in 778 Children in Colón."

KOREAN CHAPTER ORGANIZED

The Korean Chapter of the College was officially organized at an inaugural meeting held in the Dynasty Room of the Bando Hotel, Seoul, on June 16, 1958. The meeting was called to order by Dr. Eung Soo Han, Governor for the College for Korea, who gave a brief review of the activities of the College in that country. The following officers were elected:

President:	Chai Kyu Hans Lee, Seoul
1st Vice-President:	Kyung Sik Kim, Seoul
2nd Vice-President:	Chan Sae Lee, Pusan
Secretary-Treasurer:	Eung Soo Han, Seoul
Assistant Secretary-Treasurer:	Pyoung Ki Kim, Masan
Chairman, Program Committee:	Pill Whoon Hong, Seoul

Dr. Eung Soo Han was appointed official chapter representative to attend the International Congress in Tokyo.

Members of the College attending inaugural meeting of the Korean Chapter (left to right): First row: Drs. Sock H. Shin, Kyung Shik Kim, Chai Kyu H. Lee, Chan Se Lee, and Eung Soo Han; Second row: Pill Whoon Hong, Pyoung Ki Kim, Y. C. Park, Byung Suh Yu, Kiho Kim, Hi Myung Park, Lee Gap Park, N. K. Kim, and K. H. Yoo.

NEW MEXICO CHAPTER FOUNDED

On May 16, following the first scientific session presented by the New Mexico Chapter of the College, Dr. Burgess L. Gordon, Immediate Past-President of the American College of Chest Physicians, installed the New Mexico Chapter as the 73rd chapter. Dr. Carl H. Gellenthien, Valmora, was elected President; Dr. J. E. J. Harris, Albuquerque, President-Elect; Dr. Joseph Gordon, Albuquerque, Vice-President; and Dr. Roy F. Goddard, Albuquerque, Secretary-Treasurer.

At this session, charter members of the College, Drs. Carl H. Gellenthien and J. E. J. Harris, were honored at a banquet.

The New Mexico Chapter will be host to members of the College for the 25th Anniversary Homecoming Meeting to be held in Albuquerque in the fall of 1959.

Fellows of the College participating in the founding of the New Mexico Chapter (left to right): Drs. Roy F. Goddard, Albuquerque; R. Drew Miller, Rochester, Minnesota; Edwin R. Levine, Chicago; Burgess L. Gordon, Albuquerque; Albert H. Andrews, Chicago; and Mr. Murray Kornfeld, Executive Director, Chicago.

NEW CHAPTER OFFICERS

ALABAMA CHAPTER

President:	Arthur A. Calix, Decatur
Vice-President:	Justus M. Barnes, Birmingham
Secretary-Treasurer:	William J. Tally, Gadsden

CALIFORNIA CHAPTER

President:	Elmer C. Rigby, Los Angeles
Vice-President:	Thomas B. Wiper, San Francisco
Secretary-Treasurer:	Samuel J. Sills, Los Angeles

FLORIDA CHAPTER

President:	George L. Baum, Coral Gables
Vice-President:	M. Eugene Flipse, Miami
Secretary-Treasurer:	Ivan C. Schmidt, West Palm Beach

GEORGIA CHAPTER

President:	James L. Alexander, Jr., Savannah
Vice-President:	M. Bedford Davis, Jr., Atlanta
Secretary-Treasurer:	Lawrence Lee, Jr., Savannah

KANSAS CHAPTER

President:	Robert M. Brooker, Topeka
Vice-President:	John K. Fulton, Wichita
Secretary-Treasurer:	Roy A. Lawson, Chanute

MICHIGAN CHAPTER

President:	Stephen M. Gelenger, Flint
Vice-President:	Nathan Levitt, Detroit
Secretary-Treasurer:	James T. Cheng, Pontiac

MISSOURI CHAPTER

President:	David M. Skilling, Jr., St. Louis
Vice-President:	Ellis S. Lipsitz, St. Louis
Secretary-Treasurer:	David Nafe Kerr, St. Louis (re-elected)

OHIO CHAPTER

President:	Harvey Mendelsohn, Cleveland
Vice-President:	George Kress, Columbus
Secretary-Treasurer:	F. G. Kravec, Youngstown (re-elected)

OKLAHOMA CHAPTER

President:	Robert M. Shepard, Jr., Tulsa
Vice-President:	Philip M. McNeill, Oklahoma City
Secretary-Treasurer:	George L. Winn, Oklahoma City

PERU CHAPTER

President:	Mario Pastor B., Lima
Vice President:	Marino Molina, Lima
Secretary:	Alejandro A. Castro, Lima
Treasurer:	Jose Maria Almandos Velis, Lima

TEXAS CHAPTER

President:	J. Otis Armstrong, Dallas
1st Vice-President:	Lawrence M. Shefts, San Antonio
2nd Vice-President:	Hiram M. Anderson, San Angelo
Secretary-Treasurer:	Carlos J. Quintanilla, Harlingen

URUGUAY CHAPTER

President:	Juan E. Alejandro Victorica, Montevideo
Secretary-Treasurer:	René Racine, Montevideo (re-elected)

WISCONSIN CHAPTER

President:	Ross C. Kory, Wood
Vice-President:	Leon Hirsh, Milwaukee
Secretary-Treasurer:	Raymond R. Watson, Milwaukee

NEWS NOTES

The first annual Marcy Lecture, honoring **Dr. C. Howard Marcy**, Pittsburgh, Pennsylvania, was delivered by **Dr. Esmond R. Long**, former director of medical research for the National Tuberculosis Association. Dr. Marcy, a Fellow of the College, has served as the medical director of the Tuberculosis League of Pittsburgh for twenty-nine years.

Dr. William C. Voorsanger, San Francisco, was honored by the San Francisco Tuberculosis Association at its Fiftieth Anniversary Luncheon on April 1. Dr. Voorsanger received a sterling silver tray as a tribute to his many years of service as founder, director and secretary of the Association.

Prof. Dr. Aloysio de Paula, President of the Rio de Janeiro Chapter of the College and Professor of Phthisiology, University of the Federal District Medi-

cal School, Rio de Janeiro, was recently appointed Professor of Phthisiology at the State of Rio University Medical School. This appointment was made after Dr. de Paula's thesis, "Thoracoplasty and Resection in the Treatment of Pulmonary Tuberculosis" was judged the best paper in the competition for the position. Professor de Paula, one of the pioneers in Abreugraphy, is President of the Brazilian Tuberculosis Society and Director of the Tuberculosis Service of the Rio de Janeiro General Policlinic.

Prof. Dr. Manoel de Abreu, Rio de Janeiro, Brazil, Regent of the College for Southern Brazil, was recently made a member of the Order of Medical Merit and received the Great Cross of the Order in honor of his outstanding work in the field of tuberculosis and for his discovery of the method of roentgenphotography now called "Abreugraphy." His birthday, January 4, has been set aside by official government decree as "Abreugraphy Day." The Brazilian Society of Abreugraphy was organized on November 30, 1957 in the State of Rio, in which the movement to honor Prof. Abreu originated.

Dr. Sol Katz, Washington, D. C., received the first Edward Y. Davidson Award presented by the Medical Society of the District of Columbia for the best scientific paper published in the *Medical Annals of the District of Columbia* during 1957.

Dr. Arthur E. Strauss, St. Louis, Missouri, recently received the first distinguished achievement award made by the St. Louis Heart Association.

Dr. Fred M. F. Meixner, Peoria, Illinois, was awarded the Alma B. Fringer Memorial Award of the Illinois Tuberculosis Association for "truly outstanding service in the field of tuberculosis."

Dr. C. Walton Lillehei, Minneapolis, Minnesota, will receive the Oscar B. Unter Memorial Award of the American Therapeutic Society during the society's 49th annual meeting in San Francisco on June 21.

Dr. George R. Herrmann, Galveston, Texas, was recently elected Vice President of the Texas Academy of Internal Medicine.

Colonel Najib Khan, Hyderabad, West Pakistan, has been elected President of the Medical and Veterinary Section of the Pakistan Science Conference.

Dr. O. Theron Clagett, Rochester, Minnesota, was elected to honorary membership in the Irish College of Surgeons in Dublin on February 15. Dr. Clagett delivered the Abraham Colles Lecture at the Charter Day meeting of the organization.

Dr. William Likoff, Philadelphia, Pennsylvania, participated in the recent Fifth Biennial Cardiovascular Seminar of the Heart Association of Greater Miami.

The late Cardinal Stritch of Chicago conferred the Pontifical order, Knight of St. Gregory, on **Dr. John L. Keeley** of Chicago.

ANNOUNCEMENTS

A three-day international symposium on the status of tuberculosis as a public danger will be held in Philadelphia, November 20-22, at the Bellevue-Stratford Hotel, under the auspices of the Deborah Tuberculosis Sanatorium and Hospital of Browns Mills, New Jersey. Subjects to be discussed are epidemiology, mortality and morbidity changes, case finding programs, bacteriological aspects, prophylaxis including the status of BCG and isoniazid prophylaxis, surgical aspects of tuberculosis treatment, chemotherapy of tuberculosis, drug resistance, the open negative case and its various implications of public health management. Members of the planning committee are: Drs. Charles P. Bailey, Nathan Ralph, Henry Nichols, Joseph M. Fruchter and Paul K. Bornstein.

The Panray Corp., full line drug manufacturer in the human and veterinary fields, has opened a new industrial plant in Englewood, New Jersey.

MEDICAL SERVICE BUREAU

POSITION WANTED

F.C.C.P., F.A.C.S., residency-trained thoracic specialist seeks directorship of small chest hospital or chest service unit in teaching institution. Background includes 10 years full-time director chest surgical and bronchoscopic departments in large county hospital; broad administrative experience in hospital and industrial practice. Available September 1, 1958. Please address inquiries to Box 301B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Staff or resident physician wanted for 130-bed accredited tuberculosis hospital. Must have or obtain Indiana license. Salary $500 per month or more, depending upon qualifications. Family maintenance, three bedrooms, two baths, garage, food, laundry. Social Security, pension plan. Apply: Director, Healthwin Hospital. South Bend, Indiana.

Staff physician wanted immediately for large tuberculosis hospital with modern treatment of tuberculosis and concomitant illnesses. Two week vacation, liberal holiday and sick leave, and attractive retirement program. Ineligible for licensure in Texas need not apply. Salary to $11,500.00 depending on qualifications. Please address inquiries to Box 297A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

Interim Session
American College of Chest Physicians
Rochester, Minnesota, November 29-30, 1958

Semi-Annual Meeting, Board of Regents
American College of Chest Physicians
Minneapolis, Minnesota, December 1, 1958

POSTGRADUATE COURSES

13th Annual Course, "Clinical Cardiopulmonary Physiology"
Chicago, Illinois, October 13-17, 1958

11th Annual Course on Diseases of the Chest
New York City, November 10-14, 1958

CHAPTER MEETINGS

Colorado Chapter, Colorado Springs, September 28

Michigan Chapter, Detroit, October 3

Virginia Chapter, Richmond, October 12

Pacific Northwest Chapter, Vancouver, B. C., November 7-8

Potomac Chapter, Washington, D. C., November 23

Southern Chapter, New Orleans, November 2-3

Ease of operation of cylinder model Pulmonary Ventilator permits quick and effective application in therapeutic treatment of acute and chronic pulmonary disease. Where mouthpiece and nose clip are not applicable, MSA can provide a Positive Pressure Therapy Mask.

EMPHYSEMA? ASTHMA? BRONCHIECTASIS?

New M-S-A® Pulmonary Ventilator delivers pre-set positive pressure therapy during inspiration

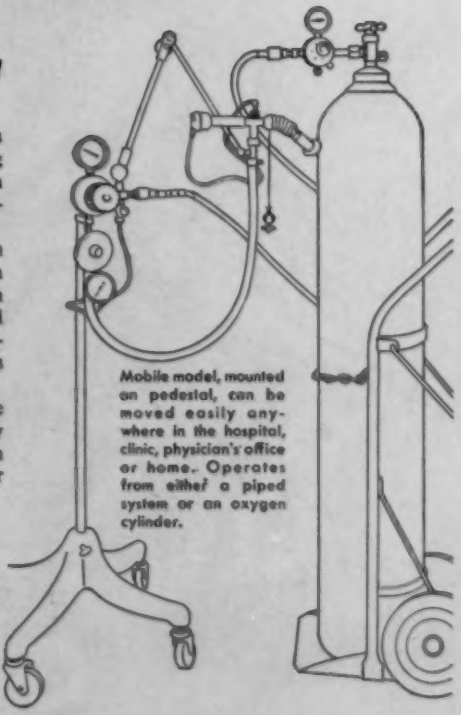
This Pulmonary Ventilator administers Intermittent Positive Pressure Breathing Inspiratory (I.P.P.B.I.), in combination with aerosol therapy, respiratory tract distribution of bronchodilators, detergents, etc.

The instrument has proved successful in bringing symptomatic relief of Emphysema and other chronic pulmonary diseases such as Asthma and Bronchiectasis. Improved model features new, easy-to-clean maintenance-free exhalation valve and supplies both dilution and 100% oxygen.

This patient-controlled demand-type valve is responsive to a slight inspiratory effort by the patient. Unit can be used with any standard oxygen cylinder. Write us for new descriptive bulletin.

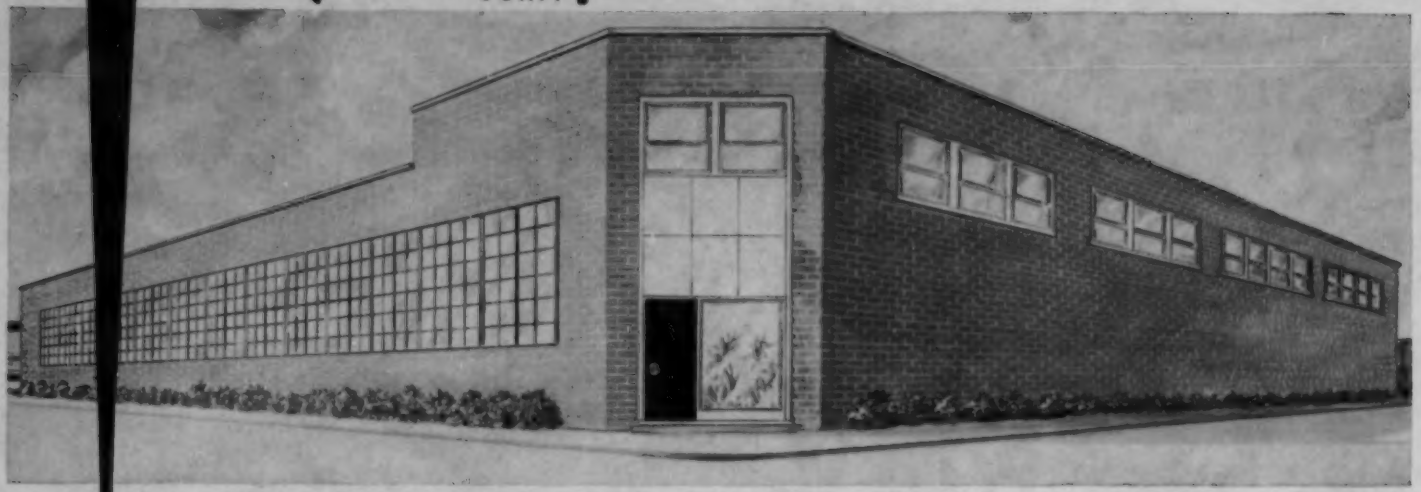
MINE SAFETY APPLIANCES COMPANY
201 North Braddock Avenue, Pittsburgh 8, Pa.

MSA
SAFETY EQUIPMENT HEADQUARTERS



Mobile model, mounted on pedestal, can be moved easily anywhere in the hospital, clinic, physician's office or home. Operates from either a piped system or an oxygen cylinder.

THE Panray CORP. announces...



266 South Dean Street, ○ Englewood, New Jersey

new, expanded plant facilities

We take this opportunity to express our warm appreciation for your continued confidence which makes our expansion possible.

Looking forward to serving you from our new headquarters.

Clara Garay
Myron Pantzer
Milton Feier

TARGET POINT CHEMOTHERAPY